=> fil capl; d que 14; d que 137;s 14 or 137; fil medl;d que 141; d que 150; s 141 or 150

FILE 'CAPLUS' ENTERED AT 16:00:47 ON 22 SEP 2000
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FILE COVERS 1967 - 22 Sep 2000 VOL 133 ISS 13
FILE LAST UPDATED: 21 Sep 2000 (20000921/ED)

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L1	388	SEA FILE=CAPLUS ABB=ON	BROOKS P?/AU
L2	147	SEA FILE=CAPLUS ABB=ON	CHERESH D?/AU
L3	157	SEA FILE=CAPLUS ABB=ON	FRIEDLANDER M?/AU
L4	4	SEA FILE=CAPLUS ABB=ON	L1 AND L2 AND L3

L1	388	SEA FILE=CAPLUS ABB=ON	BROOKS P?/AU
L2	147	SEA FILE=CAPLUS ABB=ON	CHERESH D?/AU
L3	157	SEA FILE=CAPLUS ABB=ON	FRIEDLANDER M?/AU
L5	317	SEA FILE=CAPLUS ABB=ON	.ALPHA.V.BETA.5
L6	9492	SEA FILE=CAPLUS ABB=ON	?ANGIOGEN?
L8	1243070	SEA FILE=CAPLUS ABB=ON	INHIBIT?
L11	153536	SEA FILE=CAPLUS ABB=ON	ANTAGONIST?
L16	411	SEA FILE=CAPLUS ABB=ON	ANGIOSTAT?
L30	13137	SEA FILE=CAPLUS ABB=ON	INTEGRIN#/OBI
L31	1606	SEA FILE=CAPLUS ABB=ON	L30(L)(L8 OR L11)
L37	7	SEA FILE=CAPLUS ABB=ON	((L1 OR L2 OR L3)) AND L5 AND (L6 OR L16) AND L31

L138 9 L4 OR L37

FILE 'MEDLINE' ENTERED AT 16:00:49 ON 22 SEP 2000

FILE LAST UPDATED: 15 SEP 2000 (20000915/UP). FILE COVERS 1960 TO DATE.

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The OLDMEDLINE file segment now contains data from 1958 through 1965.

Enter HELP CONTENT for details.

Left, right, and simultaneous left and right truncation are available in the Basic Index. See HELP SFIELDS for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

```
L38          532 SEA FILE=MEDLINE ABB=ON  BROOKS P?/AU
L39          128 SEA FILE=MEDLINE ABB=ON  CHERESH D?/AU
L40          306 SEA FILE=MEDLINE ABB=ON  FRIEDLANDER M?/AU
L41            2 SEA FILE=MEDLINE ABB=ON  L38 AND L39 AND L40
```

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L38          532 SEA FILE=MEDLINE ABB=ON  BROOKS P?/AU
L39          128 SEA FILE=MEDLINE ABB=ON  CHERESH D?/AU
L40          306 SEA FILE=MEDLINE ABB=ON  FRIEDLANDER M?/AU
L42          103 SEA FILE=MEDLINE ABB=ON  INTEGRIN ALPHAVBETA5/CN
L43        12309 SEA FILE=MEDLINE ABB=ON  INTEGRINS+NT/CT
L44          209 SEA FILE=MEDLINE ABB=ON  ALPHA(1W)BETA(W)5
L45          190 SEA FILE=MEDLINE ABB=ON  L43 AND (L42 OR L44)
L47        20106 SEA FILE=MEDLINE ABB=ON  ANGIOGENESIS INHIBITORS+NT/CT
L48         8543 SEA FILE=MEDLINE ABB=ON  NEOVASCULARIZATION, PATHOLOGIC+NT/CT
L50            2 SEA FILE=MEDLINE ABB=ON  ((L38 OR L39 OR L40)) AND (L47 OR
                 L48) AND L45
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L139           3 L41 OR L50
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=> fil embase; d que l64; d que l73; s l64 or l73

FILE 'EMBASE' ENTERED AT 16:01:09 ON 22 SEP 2000

FILE COVERS 1974 TO 21 Sep 2000 (20000921/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L61          522 SEA FILE=EMBASE ABB=ON  BROOKS P?/AU
L62          124 SEA FILE=EMBASE ABB=ON  CHERESH D?/AU
L63          274 SEA FILE=EMBASE ABB=ON  FRIEDLANDER M?/AU
L64            1 SEA FILE=EMBASE ABB=ON  L61 AND L62 AND L63
```

```
L61          522 SEA FILE=EMBASE ABB=ON  BROOKS P?/AU
L62          124 SEA FILE=EMBASE ABB=ON  CHERESH D?/AU
L63          274 SEA FILE=EMBASE ABB=ON  FRIEDLANDER M?/AU
L67         8718 SEA FILE=EMBASE ABB=ON  ANGIOGENESIS+NT/CT
L68         6554 SEA FILE=EMBASE ABB=ON  "NEOVASCULARIZATION (PATHOLOGY)"+NT/CT

L69        15903 SEA FILE=EMBASE ABB=ON  METALLOPROTEINASE+NT/CT
L70         8603 SEA FILE=EMBASE ABB=ON  INTEGRIN+NT/CT
L71          314 SEA FILE=EMBASE ABB=ON  ALPHA(1W)BETA(W)5
L73            4 SEA FILE=EMBASE ABB=ON  (L61 OR L62 OR L63) AND L70 AND L71
```

AND (L67 OR L68 OR L69)

L140 5 L64 OR L73

=> fil biosis; d que l96; d que l97; s l96 or l97

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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 20 September 2000 (20000920/ED)

The BIOSIS file has been reloaded. Enter HELP RLOAD and HELP REINDEXING
for details.

L90	696	SEA	FILE=BIOSIS ABB=ON	BROOKS P?/AU
L91	193	SEA	FILE=BIOSIS ABB=ON	CHERESH D?/AU
L92	473	SEA	FILE=BIOSIS ABB=ON	FRIEDLANDER M?/AU
L93	14202	SEA	FILE=BIOSIS ABB=ON	?ANGIOGEN? OR ?ANGIOSTAT?
L94	340	SEA	FILE=BIOSIS ABB=ON	ALPHA(1W)BETA(W)5
L95	15584	SEA	FILE=BIOSIS ABB=ON	INTEGRIN#
L96	9	SEA	FILE=BIOSIS ABB=ON	L94 AND L95 AND L93 AND ((L90 OR L91 OR L92))

L90	696	SEA	FILE=BIOSIS ABB=ON	BROOKS P?/AU
L91	193	SEA	FILE=BIOSIS ABB=ON	CHERESH D?/AU
L92	473	SEA	FILE=BIOSIS ABB=ON	FRIEDLANDER M?/AU
L97	4	SEA	FILE=BIOSIS ABB=ON	L90 AND L91 AND L92

L141 11 L96 OR L97

=> fil wpids; d que l124; d que l125; s l124 or l125

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>>>UPDATE WEEKS:
MOST RECENT DERWENT WEEK 200046 <200046/DW>
DERWENT WEEK FOR CHEMICAL CODING: 200046
DERWENT WEEK FOR POLYMER INDEXING: 200046
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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WPIDS, INCLUDING THE DERWENT CHEMISTRY RESOURCE (DCR),
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SEE http://www.derwent.com/covcodes.html <<<

```
L119          63 SEA FILE=WPIDS ABB=ON  BROOKS P?/AU
L120          10 SEA FILE=WPIDS ABB=ON  CHERESH D?/AU
L121           5 SEA FILE=WPIDS ABB=ON  FRIEDLANDER M?/AU
L124           2 SEA FILE=WPIDS ABB=ON  L119 AND L120 AND L121


L93        14202 SEA FILE=BIOSIS ABB=ON  ?ANGIOGEN? OR ?ANGIOSTAT?
L94          340 SEA FILE=BIOSIS ABB=ON  ALPHA(1W)BETA(W)5
L111         127 SEA FILE=BIOSIS ABB=ON  ALPHAVBETA5
L112        6987 SEA FILE=BIOSIS ABB=ON  NEOVASCUL?
L119          63 SEA FILE=WPIDS ABB=ON  BROOKS P?/AU
L120          10 SEA FILE=WPIDS ABB=ON  CHERESH D?/AU
L121           5 SEA FILE=WPIDS ABB=ON  FRIEDLANDER M?/AU
L122          68 SEA FILE=WPIDS ABB=ON  L94 OR L111
L123        2223 SEA FILE=WPIDS ABB=ON  L93 OR L112
L125           2 SEA FILE=WPIDS ABB=ON  ((L119 OR L120 OR L121)) AND L122 AND
               L123


L142           2 L124 OR L125

=> fil capl; d que l18; d que l34; s (l18 or l34) not l138

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FILE LAST UPDATED: 21 Sep 2000  (20000921/ED)

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this searchable data in CAOLD.  You now have electronic access to all
of CA: 1907 to 1966 in CAOLD and 1967 to the present in CAPLUS on STN.


L5           317 SEA FILE=CAPLUS ABB=ON  .ALPHA.V.BETA.5
L6          9492 SEA FILE=CAPLUS ABB=ON  ?ANGIOGEN?
L8       1243070 SEA FILE=CAPLUS ABB=ON  INHIBIT?
L11       153536 SEA FILE=CAPLUS ABB=ON  ANTAGONIST?
L12        11734 SEA FILE=CAPLUS ABB=ON  METALLOPROTE?
L16          411 SEA FILE=CAPLUS ABB=ON  ANGIOSTAT?
L18            4 SEA FILE=CAPLUS ABB=ON  L5 AND ((L6 AND (L8 OR L11)) OR L16)
                 AND L12
```

Searched by Barb O'Bryen, STIC 308-4291

```
L5          317 SEA FILE=CAPLUS ABB=ON  .ALPHA.V.BETA.5
L6         9492 SEA FILE=CAPLUS ABB=ON  ?ANGIOGEN?
L8      1243070 SEA FILE=CAPLUS ABB=ON  INHIBIT?
L11      153536 SEA FILE=CAPLUS ABB=ON  ANTAGONIST?
L16         411 SEA FILE=CAPLUS ABB=ON  ANGIOSTAT?
L19       25684 SEA FILE=CAPLUS ABB=ON  ?ARTHRIT?
L20      290424 SEA FILE=CAPLUS ABB=ON  ?TUMOR? OR METATSTAS?
L21       58663 SEA FILE=CAPLUS ABB=ON  RETIN? OR MACULA?
L22        2114 SEA FILE=CAPLUS ABB=ON  FIBRINOGEN#(3A)(BIND?)
L23           8 SEA FILE=CAPLUS ABB=ON  HISTOPLASMO?(5A)(OCULAR OR EYE#)
L24        3365 SEA FILE=CAPLUS ABB=ON  ?GLAUCOMA?
L25        9758 SEA FILE=CAPLUS ABB=ON  CORNEA?
L26         916 SEA FILE=CAPLUS ABB=ON  ?KERATIT?
L27         685 SEA FILE=CAPLUS ABB=ON  ?PTERYGI?
L28         215 SEA FILE=CAPLUS ABB=ON  PANNUS
L30       13137 SEA FILE=CAPLUS ABB=ON  INTEGRIN#/OBI
L31        1606 SEA FILE=CAPLUS ABB=ON  L30(L)(L8 OR L11)
L32          23 SEA FILE=CAPLUS ABB=ON  (L6 OR L16) AND L5 AND L31 AND ((L19
               OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR
               L28))
L33        1097 SEA FILE=CAPLUS ABB=ON  ANGIOGENESIS INHIBITORS/CT
L34          15 SEA FILE=CAPLUS ABB=ON  L33 AND L32


L143         11 (L18 OR L34) NOT L138

=> dup rem l139,l141,l138,l140,l142

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PROCESSING COMPLETED FOR L139
PROCESSING COMPLETED FOR L141
PROCESSING COMPLETED FOR L138
PROCESSING COMPLETED FOR L140
PROCESSING COMPLETED FOR L142
L144         16 DUP REM L139 L141 L138 L140 L142 (14 DUPLICATES REMOVED)
                ANSWERS '1-3' FROM FILE MEDLINE
                ANSWERS '4-11' FROM FILE BIOSIS
                ANSWERS '12-16' FROM FILE CAPLUS

=> d ibib ab l144 1-16


L144 ANSWER 1 OF 16  MEDLINE                              DUPLICATE 2
ACCESSION NUMBER:    1998135765     MEDLINE
                          Searched by Barb O'Bryen, STIC 308-4291
```

DOCUMENT NUMBER: 98135765
TITLE: Disruption of angiogenesis by PEX, a noncatalytic metalloproteinase fragment with integrin binding activity.
AUTHOR: **Brooks P C**; Silletti S; von Schalscha T L; **Friedlander M**; **Cheresh D A**
CORPORATE SOURCE: Department of Immunology, The Scripps Research Institute, La Jolla, California 92037, USA.
CONTRACT NUMBER: HL54444 (NHLBI)
CA50286 (NCI)
CA45726 (NCI)
+
SOURCE: CELL, (1998 Feb 6) 92 (3) 391-400.
Journal code: CQ4. ISSN: 0092-8674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199805
AB Angiogenesis depends on both cell adhesion and proteolytic mechanisms. In fact, matrix metalloproteinase 2 (MMP-2) and integrin alphavbeta3 are functionally associated on the surface of angiogenic blood vessels. A fragment of MMP-2, which comprises the C-terminal hemopexin-like domain, termed PEX, prevents this enzyme binding to alphavbeta3 and blocks cell surface collagenolytic activity. PEX blocks MMP-2 activity on the chick chorioallantoic membrane where it disrupts angiogenesis and tumor growth. Importantly, a naturally occurring form of PEX can be detected in vivo in conjunction with alphavbeta3 expression in tumors and during developmental retinal neovascularization. Levels of PEX in these vascularized tissues suggest that it interacts with endothelial cell alphavbeta3 where it serves as a natural inhibitor of MMP-2 activity, thereby regulating the invasive behavior of new blood vessels.

DUPLICATE 6

L144 ANSWER 2 OF 16 MEDLINE
ACCESSION NUMBER: 96382541 MEDLINE
DOCUMENT NUMBER: 96382541
TITLE: Involvement of integrins alpha v beta 3 and **alpha** v **beta 5** in ocular neovascular diseases.
AUTHOR: **Friedlander M**; Theesfeld C L; Sugita M; Fruttiger M; Thomas M A; Chang S; **Cheresh D A**
CORPORATE SOURCE: Department of Cell Biology, Scripps Research Institute, La Jolla, CA 92037, USA.
CONTRACT NUMBER: EY 11254 (NEI)
HL 54444 (NHLBI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Sep 3) 93 (18) 9764-9.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199612
AB Angiogenesis underlies the majority of eye diseases that result in catastrophic loss of vision. Recent evidence has implicated the integrins alpha v beta 3 and **alpha** v **beta 5** in the angiogenic process. We examined the expression of alpha v beta 3 and **alpha** v **beta 5** in neovascular ocular tissue from patients with subretinal neovascularization from age-related macular degeneration or the presumed ocular histoplasmosis syndrome or retinal neovascularization from proliferative diabetic retinopathy (PDR). Only alpha v beta 3 was observed on blood vessels in ocular tissues with active neovascularization from patients with age-related macular degeneration or

presumed ocular histoplasmosis, whereas both alpha v beta 3 and **alpha** v **beta 5** were present on vascular cells in tissues from patients with PDR. Since we observed both integrins on vascular cells from tissues of patients with retinal neovascularization from PDR, we examined the effects of a systemically administered cyclic peptide antagonist of alpha v beta 3 and **alpha** v **beta 5** on retinal angiogenesis in a murine model. This antagonist specifically blocked new blood vessel formation with no effect on established vessels. These results not only reinforce the concept that retinal and subretinal neovascular diseases are distinct pathological processes, but that antagonists of alpha v beta 3 and/or **alpha** v **beta 5** may be effective in treating individuals with blinding eye disease associated with angiogenesis.

L144 ANSWER 3 OF 16 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 96095214 MEDLINE
DOCUMENT NUMBER: 96095214
TITLE: Definition of two angiogenic pathways by distinct alpha v integrins.
AUTHOR: **Friedlander M; Brooks P C**; Shaffer R W; Kincaid C M; Varner J A; **Cheresh D A**
CORPORATE SOURCE: Robert Mealey Laboratory for the Study of Macular Degenerations, Department of Cell Biology, Scripps Research Institute, La Jolla, CA 92037, USA.
SOURCE: SCIENCE, (1995 Dec 1) 270 (5241) 1500-2.
Journal code: UJ7. ISSN: 0036-8075.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199603
AB Angiogenesis depends on cytokines and vascular cell adhesion events. Two cytokine-dependent pathways of angiogenesis were shown to exist and were defined by their dependency on distinct vascular cell integrins. In vivo angiogenesis in corneal or chorioallantoic membrane models induced by basic fibroblast growth factor or by tumor necrosis factor-alpha depended on alpha v beta 3, whereas angiogenesis initiated by vascular endothelial growth factor, transforming growth factor-alpha, or phorbol ester depended on **alpha** v **beta 5**. Antibody to each integrin selectively blocked one of these pathways, and a cyclic peptide antagonist of both integrins blocked angiogenesis stimulated by each cytokine tested. These pathways are further distinguished by their sensitivity to calphostin C, an inhibitor of protein kinase C that blocked angiogenesis potentiated by **alpha** v **beta 5** but not by alpha v beta 3.

L144 ANSWER 4 OF 16 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 5
ACCESSION NUMBER: 1997:13452 BIOSIS
DOCUMENT NUMBER: PREV199799312655
TITLE: Requirement of receptor-bound urokinase-type plasminogen activator for **integrin alpha**-v-**beta-5**-directed cell migration.
AUTHOR(S): Yebra, Mayra; Parry, Graham C. N.; Stroemblad, Staffan; Mackman, Nigel; Rosenberg, Steven; Mueller, Barbara M.; **Cheresh, David A. (1)**
CORPORATE SOURCE: (1) Dep. Immunol. Vascular Biol., Scripps Res. Inst., IMM24 10666 N. Torrey Pines Rd., La Jolla, CA 92037 USA
SOURCE: Journal of Biological Chemistry, (1996) Vol. 271, No. 46, pp. 29393-29399.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
Searched by Barb O'Bryen, STIC 308-4291

AB The urokinase plasminogen activator (uPA) interacts with its cell surface receptor (uPAR), providing an inducible, localized cell surface proteolytic activity, thereby promoting cellular invasion. Evidence is provided for a novel function of cell surface-associated uPA cntdot uPAR. Specifically, induction of cell surface expression of uPA cntdot uPAR by growth factors or phorbol ester was necessary for vitronectin-dependent carcinoma cell migration, an event mediated by **integrin alpha**-v-**beta-5**. Cell migration on vitronectin was blocked with either a soluble form of uPAR, an antibody that disrupts uPA binding to uPAR, or a monoclonal antibody to **alpha**-v-**beta-5**. Moreover, plasminogen activator inhibitor type 2 blocked this migration event but did not affect adhesion, suggesting a direct role for uPA enzyme activity in this process and that migration but not adhesion of these cells is regulated by uPA cntdot uPAR. Growth factor-mediated induction of uPA cntdot uPAR on the carcinoma cell surface promotes a specific motility event mediated by **integrin alpha**-v-**beta-5**, since cells transfected with the beta-3 **integrin** subunit expressed alpha-v-beta-3 and migrated on vitronectin independently of growth factors or uPA cntdot uPAR expression. This relationship between **alpha**-v-**beta-5** and the uPA cntdot uPAR system has significant implications for regulation of motility events associated with development, **angiogenesis**, and tumor metastasis.

L144 ANSWER 5 OF 16 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 7
ACCESSION NUMBER: 1996:312908 BIOSIS
DOCUMENT NUMBER: PREV199699035264
TITLE: Transient functional expression of alpha-v-beta-3 on vascular cells during wound repair.
AUTHOR(S): Clark, Richard A. F. (1); Tonnesen, Marcia G.; Gailit, James; **Cheresh, David A.**
CORPORATE SOURCE: (1) Dep. Dermatol., SUNY at Stony Brook, Stony Brook, NY 11794-8165 USA
SOURCE: American Journal of Pathology, (1996) Vol. 148, No. 5, pp. 1407-1421.
ISSN: 0002-9440.
DOCUMENT TYPE: Article
LANGUAGE: English

AB During early granulation tissue formation of wound repair, new capillaries invade the fibrin clot, a process that undoubtedly requires an interaction of vascular cells with the wound provisional matrix composed mainly of fibrin, fibronectin, and vitronectin. **Integrin** alpha-v beta-3 is the vascular cell receptor for these wound-associated adhesive proteins. Therefore, we investigated the expression of this receptor on new capillaries of beating full-thickness cutaneous porcine wounds. During granulation tissue formation, alpha-v beta-3 was expressed specifically on capillary sprouts invading the central fibrin clot whereas the closely related **integrin alpha**-v **beta-5** failed to localize to these cells. Cyclic peptides or antibody antagonists of alpha-v beta-3 specifically inhibited granulation tissue formation in a transient manner during the period of invasive **angiogenesis**. Immunolocalization studies revealed that alpha-v beta-3 became aggregated and lost from sprouting vessels after treatment with a peptide antagonist. In contrast, beta-1 **integrins** were not modulated by this treatment. Once granulation tissue filled the wound and invasive **angiogenesis** terminated, the alpha-v beta-3 showed little or no expression in the granulation tissue microvasculature. These data demonstrate that **integrin** alpha-v beta-3 plays a fundamental, but transient, role during invasive **angiogenesis** and granulation tissue formation in a healing wound.

L144 ANSWER 6 OF 16 BIOSIS COPYRIGHT 2000 BIOSIS
Searched by Barb O'Bryen, STIC 308-4291

ACCESSION NUMBER: 1999:44592 BIOSIS
DOCUMENT NUMBER: PREV199900044592
TITLE: Requirement for SRC activity during VEGF but not BFGF-induced **angiogenesis**.
AUTHOR(S): Eliceiri, Brian P. (1); Andrews, Catherine; Schwartzerg, Pamela L.; **Cheresh, David A.**
CORPORATE SOURCE: (1) Dep. Immunology, Scripps Res. Inst., La Jolla, CA USA
SOURCE: Molecular Biology of the Cell, (Nov., 1998) Vol. 9, No. SUPPL., pp. 422A.
Meeting Info.: 38th Annual Meeting of the American Society for Cell Biology San Francisco, California, USA December 12-16, 1998 American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L144 ANSWER 7 OF 16 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:194530 BIOSIS
DOCUMENT NUMBER: PREV199800194530
TITLE: Antagonists of **integrin** alphavbeta3/alphavbeta5: An anti-**angiogenic** strategy for the treatment of cancer.
AUTHOR(S): Mohler, T. (1); **Brooks, P. C.**; Mitjans, F.; Jonczyk, A.; Goodman, S.; **Cheresh, D. A.**
CORPORATE SOURCE: (1) Scripps Res. Inst., La Jolla, CA 92037 USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1998) Vol. 39, pp. 97.
Meeting Info.: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998 American Association for Cancer Research
. ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L144 ANSWER 8 OF 16 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:67571 BIOSIS
DOCUMENT NUMBER: PREV199800067571
TITLE: Role of endothelial cell **integrins** alphavbeta3 and alphavbeta5 in the **angiogenic** response of tumors.
AUTHOR(S): Mohler, T.; **Brooks, P. C.**; **Cheresh, D. A.**
CORPORATE SOURCE: Scripps Res. Inst., San Diego, CA USA
SOURCE: Blood, (Nov. 15, 1997) Vol. 90, No. 10 SUPPL. 1 PART 1, pp. 286A.
Meeting Info.: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997 The American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L144 ANSWER 9 OF 16 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1996:484509 BIOSIS
DOCUMENT NUMBER: PREV199699199765
TITLE: Protein kinase C regulates **alpha**-v-**beta**-**5**-dependent cytoskeletal associations and focal adhesion kinase phosphorylation.
AUTHOR(S): Lewis, J. M.; **Cheresh, D. A.**; Schwartz, M. A. (1)
CORPORATE SOURCE: (1) Dep. Vascular Biol., Scripps Research Inst., 10666 North Torrey Pines Road, La Jolla, CA 92037 USA
SOURCE: Journal of Cell Biology, (1996) Vol. 134, No. 5, pp.

1323-1332.
ISSN: 0021-9525.
DOCUMENT TYPE: Article
LANGUAGE: English
AB **Integrins** alpha-v-beta-3 and alpha-vp5 both mediate cell adhesion to vitronectin yet trigger different postligand binding events. **Integrin** alpha-v-beta-3 is able to induce cell spreading, migration, **angiogenesis**, and tumor metastasis without additional stimulators, whereas alpha-v-beta-3 requires exogenous activation of protein kinase C (PKC) to mediate these processes. To investigate this difference, the ability of beta-3 or beta-5 to induce colocalization of intracellular proteins was assessed by immunofluorescence in hamster CS-1 melanoma cells. We found that **alpha-v-beta-5** induced colocalization of talin, alpha-actinin, tensin, and actin very weakly relative to alpha-v-beta-3. **alpha-v-beta-5** was able to efficiently induce colocalization of focal adhesion kinase (FAK); however, it was unable to increase phosphorylation of FAK on tyrosine. Activation of PKC by adding phorbol ester to **alpha-v-beta-5**-expressing cells induced spreading, increased colocalization of alpha-actinin, tensin, vinculin, p130-cas and actin, and triggered tyrosine phosphorylation of FAK. Unexpectedly, talin colocalization remained low even after activation of PKC. Treatment of cells with the PKC inhibitor calphostin C inhibited spreading and the colocalization of talin, alpha-actinin, tensin, and actin for both alpha-v-beta-3 and **alpha-v-beta-5**. We conclude that PKC regulates localization of cytoskeletal proteins and phosphorylation of FAK induced by **alpha-v-beta-5**. Our results also show that FAK can be localized independent of its phosphorylation and that cells can spread and induce localization of other focal adhesion proteins in the absence of detectable talin.

L144 ANSWER 10 OF 16 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1996:200667 BIOSIS
DOCUMENT NUMBER: PREV199698756796
TITLE: **Integrins** alpha-beta-3 and **alpha-beta-5** are selectively expressed in active human retinal and choroidal neovascular membranes.
AUTHOR(S): **Friedlander, M. (1)**; Theesfeld, C. L. (1); Sugita, M. (1); Thomas, M. A.; Chang, S.; Coll, G.; Fruttiger, M. A.; Richardson, W. D.; **Brooks, P. C.**; **Cheresh, D. A.**
CORPORATE SOURCE: (1) Dep. Cell Biology, Scripps Res. Inst., St. Louis, MO USA
SOURCE: Investigative Ophthalmology & Visual Science, (1996) Vol. 37, No. 3, pp. S124.
Meeting Info.: 1996 Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA April 21-26, 1996
ISSN: 0146-0404.
DOCUMENT TYPE: Conference
LANGUAGE: English

L144 ANSWER 11 OF 16 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1995:236200 BIOSIS
DOCUMENT NUMBER: PREV199598250500
TITLE: An antibody to the integrin alpha-v-beta-3 inhibits ocular angiogenesis.
AUTHOR(S): **Friedlander, M.**; Shaffer, R.; Kincaid, C.; **Brooks, P.**; **Cheresh, D.**
CORPORATE SOURCE: Dep. Cell Biology, Scripps Res. Inst., La Jolla, CA USA
SOURCE: Investigative Ophthalmology & Visual Science, (1995) Vol. 36, No. 4, pp. S1047.

Meeting Info.: Annual Meeting of the Investigative Ophthalmology and Visual Science Fort Lauderdale, Florida, USA May 14-19, 1995
ISSN: 0146-0404.
DOCUMENT TYPE: Conference
LANGUAGE: English

L144 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 1
ACCESSION NUMBER: 1998:617874 CAPLUS
DOCUMENT NUMBER: 129:330990
TITLE: Design, synthesis and biological evaluation of nonpeptide **integrin antagonists**
AUTHOR(S): Nicolaou, K. C.; Trujillo, John I.; Jandeleit, Bernd; Chibale, Kelly; Rosenfeld, M.; Diefenbach, B.; **Cheresh, D. A.**; Goodman, S. L.
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Bioorg. Med. Chem. (1998), 6(8), 1185-1208
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent studies demonstrated that peptide and antibody antagonists of integrin .alpha.v.beta.3 block **angiogenesis** and tumor growth. In this article, the design, synthesis and biol. evaluation of a series of nitroaryl ether-based, non-peptide mimetics are described. The design of these compds. was based on Merck's aryl ether/.alpha.-amino acid/guanidine framework and incorporates a novel nitroaryl system. The synthesized mimetics were tested against a variety of integrins (.alpha.v.beta.3, .alpha.IIb.beta.3, and .**alpha.v.beta.**
5) in order to det. their binding selectivity and ability to inhibit cell adhesion. Selected compds. were also tested for their ability to inhibit **angiogenesis** in vivo in the CAM (chick chorioallantoic membrane) assay. From the generated compd. library, compds. two proved to be potent and selective inhibitors of .alpha.IIb.beta.3 (IC50 = 14 nM) whereas one compd. showed excellent in vivo inhibition of **angiogenesis** (at 30 .mu.g/embryo).

L144 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 3
ACCESSION NUMBER: 1997:805756 CAPLUS
DOCUMENT NUMBER: 128:48501
TITLE: Preparation of cyclopeptides, sulfonyltyrosine derivatives, and monoclonal antibodies as antitumor agents and .**alpha.v.beta**
.**5** mediated **angiogenesis** inhibitors for treatment of eye diseases
INVENTOR(S): **Brooks, Peter; Cheresh, David A.; Friedlander, Martin**
PATENT ASSIGNEE(S): Scripps Research Institute, USA; Brooks, Peter; Cheresh, David A.; Friedlander, Martin
SOURCE: PCT Int. Appl., 121 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9745447	A1	19971204	WO 1997-US9099	19970530

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,

DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,
PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, US,
UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN,
ML, MR, NE, SN, TD, TG

AU 9732183	A1	19980105	AU 1997-32183	19970530
EP 907661	A1	19990414	EP 1997-927814	19970530
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9709514	A	19990810	BR 1997-9514	19970530
CN 1226254	A	19990818	CN 1997-196818	19970530
CN 1226172	A	19990818	CN 1997-196822	19970530
NO 9805575	A	19990201	NO 1998-5575	19981127
PRIORITY APPLN. INFO.:			US 1996-15869	19960531
			US 1996-18733	19960531
			WO 1997-US9099	19970530

AB The present invention describes methods for inhibiting **angiogenesis** in tissues using vitronectin .**alpha**. **v**.**beta**.**5** antagonists. The .**alpha**. **v**.**beta**.**5**-mediated **angiogenesis** is correlated with exposure to cytokines including vascular endothelial growth factor, transforming growth factor-.alpha. and epidermal growth factor. Inhibition of .**alpha**.**v**.**beta**. **5**-mediated **angiogenesis** is particularly preferred in vascular endothelial ocular neovascular diseases, in tumor growth and in inflammatory conditions, using therapeutic compns. contg. .**alpha** .**v**.**beta**.**5** antagonists. Thus, cyclopeptide cyclo(Arg-Asp-Gly-D-Phe-N-MeVal) (I) was prepd. by std. solid-phase methods using 9-fluorenylmethoxycarbonyl (Fmoc) chem. I and related RGD cyclopeptides, as well as N-sulfonyl-O-guanidinylalkyltyrosine derivs., monoclonal antibodies, and synthetic matrix metalloproteins peptides and fusion proteins were tested for **angiogenesis** inhibition in a no. of models, including an in vivo rabbit eye model.

L144 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 4

ACCESSION NUMBER: 1997:265569 CAPLUS
DOCUMENT NUMBER: 126:251416
TITLE: Preparation of tyrosine derivatives as compounds useful for **inhibition** of vitronectin . **alpha**.**v**.**beta**.**5** **integrin**-mediated **angiogenesis**
INVENTOR(S): **Brooks, Peter**; **Cheresh, David A.**; **Friedlander, Martin**
PATENT ASSIGNEE(S): Scripps Research Institute, USA; Brooks, Peter; Cheresh, David A.; Friedlander, Martin
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9706791	A1	19970227	WO 1996-US13194	19960813

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM

AU 9668466	A1	19970312	AU 1996-68466	19960813
EP 844874	A1	19980603	EP 1996-928868	19960813
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
CN 1198667	A	19981111	CN 1996-197429	19960813
JP 11511171	T2	19990928	JP 1996-509460	19960813
NO 9800622	A	19980407	NO 1998-622	19980213
PRIORITY APPLN. INFO.:			US 1995-514799	19950814
			WO 1996-US13194	19960813

AB The present invention describes methods for inhibiting **angiogenesis** in tissues using vitronectin .**alpha**.**v**.**beta**.**5** antagonists. The .**alpha**.**v**.**beta**.**5**-mediated **angiogenesis** is correlated with exposure to cytokines including vascular endothelial growth factor, transforming growth factor-.alpha. and epidermal growth factor. Inhibition of .**alpha**.**v**.**beta**.**5**-mediated **angiogenesis** is particularly preferred in vascular endothelial ocular neovascular diseases, in tumor growth and in inflammatory conditions, using therapeutic compns. contg. .**alpha**.**v**.**beta**.**5** antagonists. Thus, Boc-Tyr-OCH2Ph (prepn. given) was converted in 6 steps into guanidino deriv. I. I and related guanidine and amidine derivs. were useful as **angiogenesis** inhibitors.

L144 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER:	1999:37953 CAPLUS
DOCUMENT NUMBER:	130:232144
TITLE:	Decreased **angiogenesis** and arthritic disease in rabbits treated with an .alpha.v.beta.3 antagonist
AUTHOR(S):	Storgard, Chris M.; Stupack, Dwayne G.; Jonczyk, Alfred; Goodman, Simon L.; Fox, Robert I.; **Cheresh, David A.**
CORPORATE SOURCE:	Departments of Immunology and Vascular Biology (IMM24), The Scripps Research Institute, LaJolla, CA, 92037, USA
SOURCE:	J. Clin. Invest. (1999), 103(1), 47-54 CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER:	American Society for Clinical Investigation
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Rheumatoid arthritis (RA) is an inflammatory disease assocd. with intense **angiogenesis** and vascular expression of integrin .alpha.v.beta.3. Intra-articular administration of a cyclic peptide antagonist of integrin .alpha.v.beta.3 to rabbits with antigen-induced arthritis early in disease resulted in inhibition of synovial **angiogenesis** and reduced synovial cell infiltrate, pannus formation, and cartilage erosions. These effects were not assocd. with lymphopenia or impairment of leukocyte function. Furthermore, when administered in chronic, preexisting disease, the .alpha.v.beta.3 antagonist effectively diminished arthritis severity and was assocd. with a quant. increase in apoptosis of the **angiogenic** blood vessels. Therefore, **angiogenesis** appears to be a central factor in the initiation and persistence of arthritic disease, and antagonists of integrin .alpha.v.beta.3 may represent a novel therapeutic strategy for RA.

REFERENCE COUNT: 39

REFERENCE(S):

(1) Andreesen, R; J Leukoc Biol 1990, V47, P490 CAPLUS
(3) Aumailley, M; FEBS Lett 1991, V291, P50 CAPLUS
(4) Brooks, P; Cell 1994, V79, P1157 CAPLUS
(5) Brooks, P; J Clin Invest 1995, V96, P1815 CAPLUS
(6) Brooks, P; Science 1994, V264, P569 CAPLUS

Searched by Barb O'Bryen, STIC 308-4291

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L144 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:803827 CAPLUS
DOCUMENT NUMBER: 128:48497
TITLE: Preparation of cyclopeptides, fusion proteins, monoclonal antibodies, and sulfonyltyrosine derivs. as .**alpha**.**v**.**beta**.**5** mediated **angiogenesis** inhibitors and antitumor agents
INVENTOR(S): **Brooks, Peter; Cheresh, David A.**
PATENT ASSIGNEE(S): Scripps Research Institute, USA; Brooks, Peter; Cheresh, David A.
SOURCE: PCT Int. Appl., 234 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9745137	A1	19971204	WO 1997-US9158	19970530
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9732893	A1	19980105	AU 1997-32893	19970530
CN 1226254	A	19990818	CN 1997-196818	19970530
CN 1226172	A	19990818	CN 1997-196822	19970530
EP 951295	A1	19991027	EP 1997-928698	19970530
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 9805574	A	19990201	NO 1998-5574	19981127
PRIORITY APPLN. INFO.:			US 1996-15869	19960531
			US 1996-18733	19960531
			WO 1997-US9158	19970530

AB The present invention describes methods for inhibiting **angiogenesis** in tissues using vitronectin .**alpha**.**v**.**beta**.**5** antagonists. The .**alpha**.**v**.**beta**.**5**-mediated **angiogenesis** is correlated with exposure to cytokines including vascular endothelial growth factor, transforming growth factor-.alpha. and epidermal growth factor. Inhibition of .**alpha**.**v**.**beta**.**5**-mediated **angiogenesis** is particularly preferred in vascular endothelial ocular neovascular diseases, in tumor growth and in inflammatory conditions, using therapeutic compns. contg. .**alpha**.**v**.**beta**.**5** antagonists. Thus, cyclopeptide cyclo(Arg-Asp-Gly-D-Phe-N-MeVal) (I) was prepd. by std. solid-phase methods using 9-fluorenylmethoxycarbonyl (Fmoc) chem. I and related RGD cyclopeptides, as well as N-sulfonyl-O-guanidinylalkyltyrosine derivs., monoclonal antibodies, and synthetic matrix metalloproteins peptides and fusion proteins were tested for **angiogenesis** inhibition in a no. of antitumor models.

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=> fil capl; d que l18; d que l34; s (l18 or l34) not l1138

FILE 'CAPLUS' ENTERED AT 16:03:54 ON 22 SEP 2000
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FILE COVERS 1967 - 22 Sep 2000  VOL 133 ISS 13
FILE LAST UPDATED: 21 Sep 2000  (20000921/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

  This file supports REGlstRY for direct browsing and searching of
  all substance data from the REGISTRY file.  Enter HELP FIRST for
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Now you can extend your author, patent assignee, patent information,
and title searches back to 1907.  The records from 1907-1966 now have
this searchable data in CAOLD.  You now have electronic access to all
of CA: 1907 to 1966 in CAOLD and 1967 to the present in CAPLUS on STN.


L5          317 SEA FILE=CAPLUS ABB=ON  .ALPHA.V.BETA.5
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L8      1243070 SEA FILE=CAPLUS ABB=ON  INHIBIT?
L11      153536 SEA FILE=CAPLUS ABB=ON  ANTAGONIST?
L12       11734 SEA FILE=CAPLUS ABB=ON  METALLOPROTE?
L16         411 SEA FILE=CAPLUS ABB=ON  ANGIOSTAT?
L18           4 SEA FILE=CAPLUS ABB=ON  L5 AND ((L6 AND (L8 OR L11)) OR L16)
                AND L12



L5          317 SEA FILE=CAPLUS ABB=ON  .ALPHA.V.BETA.5
L6         9492 SEA FILE=CAPLUS ABB=ON  ?ANGIOGEN?
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L20      290424 SEA FILE=CAPLUS ABB=ON  ?TUMOR? OR METATSTAS?
L21       58663 SEA FILE=CAPLUS ABB=ON  RETIN? OR MACULA?
L22        2114 SEA FILE=CAPLUS ABB=ON  FIBRINOGEN#(3A)(BIND?)
L23           8 SEA FILE=CAPLUS ABB=ON  HISTOPLASMO?(5A)(OCULAR OR EYE#)
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L25        9758 SEA FILE=CAPLUS ABB=ON  CORNEA?
L26         916 SEA FILE=CAPLUS ABB=ON  ?KERATIT?
L27         685 SEA FILE=CAPLUS ABB=ON  ?PTERYGI?
L28         215 SEA FILE=CAPLUS ABB=ON  PANNUS
L30       13137 SEA FILE=CAPLUS ABB=ON  INTEGRIN#/OBI
L31        1606 SEA FILE=CAPLUS ABB=ON  L30(L)(L8 OR L11)
L32          23 SEA FILE=CAPLUS ABB=ON  (L6 OR L16) AND L5 AND L31 AND ((L19
                OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR
                L28))
L33        1097 SEA FILE=CAPLUS ABB=ON  ANGIOGENESIS INHIBITORS/CT
                      Searched by Barb O'Bryen, STIC 308-4291
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L34          15 SEA FILE=CAPLUS ABB=ON  L33 AND L32

L145         11 (L18 OR L34) NOT (L138)  previously printed

=> fil medl; d que 166

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 FILE LAST UPDATED: 15 SEP 2000 (20000915/UP).  FILE COVERS 1960 TO DATE.

 MEDLINE has been reloaded to reflect the annual MeSH changes made by
 the National Library of Medicine for 2000. Enter HELP RLOAD for details.

 The OLDMEDLINE file segment now contains data from 1958 through 1965.
 Enter HELP CONTENT for details.

 Left, right, and simultaneous left and right truncation are available in the
 Basic Index.  See HELP SFIELDS for details.

 THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE
 SUBSTANCE IDENTIFICATION.


L42          103 SEA FILE=MEDLINE ABB=ON  INTEGRIN ALPHAVBETA5/CN
L43        12309 SEA FILE=MEDLINE ABB=ON  INTEGRINS+NT/CT
L44          209 SEA FILE=MEDLINE ABB=ON  ALPHA(1W)BETA(W)5
L45          190 SEA FILE=MEDLINE ABB=ON  L43 AND (L42 OR L44)
L65        20556 SEA FILE=MEDLINE ABB=ON  METALLOENDOPEPTIDASES+NT/CT
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=> d que l150

L42          103 SEA FILE=MEDLINE ABB=ON  INTEGRIN ALPHAVBETA5/CN
L43        12309 SEA FILE=MEDLINE ABB=ON  INTEGRINS+NT/CT
L44          209 SEA FILE=MEDLINE ABB=ON  ALPHA(1W)BETA(W)5
L45          190 SEA FILE=MEDLINE ABB=ON  L43 AND (L42 OR L44)
L47        20106 SEA FILE=MEDLINE ABB=ON  ANGIOGENESIS INHIBITORS+NT/CT
L48         8543 SEA FILE=MEDLINE ABB=ON  NEOVASCULARIZATION, PATHOLOGIC+NT/CT
L51            9 SEA FILE=MEDLINE ABB=ON  L45 AND (L47 OR L48)
L52       109370 SEA FILE=MEDLINE ABB=ON  ARTHRITIS+NT/CT
L53        44940 SEA FILE=MEDLINE ABB=ON  RETINAL DISEASES+NT/CT
L54        19008 SEA FILE=MEDLINE ABB=ON  FIBRINOGEN/CT
L55          227 SEA FILE=MEDLINE ABB=ON  GLAUCOMA, NEOVASCULAR/CT
L56          832 SEA FILE=MEDLINE ABB=ON  PTERYGIUM/CT
L57        10342 SEA FILE=MEDLINE ABB=ON  KERATITIS+NT/CT
L58         6679 SEA FILE=MEDLINE ABB=ON  CORNEAL TRANSPLANTATION+NT/CT
L60            9 SEA FILE=MEDLINE ABB=ON  L45 AND ((L52 OR L53 OR L54 OR L55 OR
                 L56 OR L57 OR L58))
L147      515264 SEA FILE=MEDLINE ABB=ON  PEPTIDES+NT/CT
L148      237695 SEA FILE=MEDLINE ABB=ON  AMINO ACID SEQUENCE+NT/CT
L150           8 SEA FILE=MEDLINE ABB=ON  (L60 OR L51) AND (L147 OR L148)

=> s (l150 or l66) not l139

L151        10 (L150 OR L66) NOT (L139)  previously printed

=> fil embase; d que 175; d que 188; s (175 or 188) not 1140
                    Searched by Barb O'Bryen, STIC 308-4291
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FILE 'EMBASE' ENTERED AT 16:07:36 ON 22 SEP 2000

FILE COVERS 1974 TO 21 Sep 2000 (20000921/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L75           4 SEA FILE=EMBASE ABB=ON  L71 AND L70 AND L69


L67        8718 SEA FILE=EMBASE ABB=ON  ANGIOGENESIS+NT/CT
L68        6554 SEA FILE=EMBASE ABB=ON  "NEOVASCULARIZATION (PATHOLOGY)"+NT/CT

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L78       83486 SEA FILE=EMBASE ABB=ON  ARTHRITIS+NT/CT
L79       51680 SEA FILE=EMBASE ABB=ON  RETINA DISEASE+NT/CT
L80        8631 SEA FILE=EMBASE ABB=ON  KERATITIS+NT/CT
L81         715 SEA FILE=EMBASE ABB=ON  PTERYGIUM+NT/CT
L82          35 SEA FILE=EMBASE ABB=ON  OCULAR HISTOPLASMOSIS/CT
L83         237 SEA FILE=EMBASE ABB=ON  PANNUS/CT
L84        3371 SEA FILE=EMBASE ABB=ON  CORNEA TRANSPLANTATION+NT/CT
L85       18516 SEA FILE=EMBASE ABB=ON  GLAUCOMA+NT/CT
L86       13657 SEA FILE=EMBASE ABB=ON  FIBRINOGEN/CT
L88           6 SEA FILE=EMBASE ABB=ON  L70 AND L71 AND ((L77 OR L78 OR L79 OR
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                L68)


L152          8 (L75 OR L88) NOT L140   previously printed
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 20 September 2000 (20000920/ED)

The BIOSIS file has been reloaded. Enter HELP RLOAD and HELP REINDEXING for details.

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L94         340 SEA FILE=BIOSIS ABB=ON  ALPHA(1W)BETA(W)5
L95       15584 SEA FILE=BIOSIS ABB=ON  INTEGRIN#
L98       12825 SEA FILE=BIOSIS ABB=ON  METALLOPROT?
L111        127 SEA FILE=BIOSIS ABB=ON  ALPHAVBETA5
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Searched by Barb O'Bryen, STIC 308-4291

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                 L95 AND L98


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L95        15584 SEA FILE=BIOSIS ABB=ON  INTEGRIN#
L100       26359 SEA FILE=BIOSIS ABB=ON  FIBRINOGEN?
L101       76395 SEA FILE=BIOSIS ABB=ON  ?ARTHRITI?
L102      806036 SEA FILE=BIOSIS ABB=ON  TUMOR? OR ?NEOPLAS? OR METASTAT?
L103       17987 SEA FILE=BIOSIS ABB=ON  ?RETINOPATH? OR MACULAR DEGENERATION
L104        4059 SEA FILE=BIOSIS ABB=ON  ?HISTOPLASM?
L105       18663 SEA FILE=BIOSIS ABB=ON  ?GLAUCOM?
L106       33258 SEA FILE=BIOSIS ABB=ON  CORNEA?
L107        4531 SEA FILE=BIOSIS ABB=ON  ?KERATITI?
L108        3690 SEA FILE=BIOSIS ABB=ON  ?PTERYGI?
L109         667 SEA FILE=BIOSIS ABB=ON  PANNUS
L111         127 SEA FILE=BIOSIS ABB=ON  ALPHAVBETA5
L112        6987 SEA FILE=BIOSIS ABB=ON  NEOVASCUL?
L115     1035625 SEA FILE=BIOSIS ABB=ON  INHIBIT? OR ANTAGONI?
L117        1501 SEA FILE=BIOSIS ABB=ON  L95(8A)L115
L118          12 SEA FILE=BIOSIS ABB=ON  (L94 OR L111) AND (L93 OR L112) AND
                 L117 AND ((L100 OR L101 OR L102 OR L103 OR L104 OR L105 OR
                 L106 OR L107 OR L108 OR L109))


L153          12 (L113 OR L118) NOT L141   previously printed

=> fil wpids;d que l134; d que l135; s (l134 or l135) not l142

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L93        14202 SEA FILE=BIOSIS ABB=ON  ?ANGIOGEN? OR ?ANGIOSTAT?
L94          340 SEA FILE=BIOSIS ABB=ON  ALPHA(1W)BETA(W)5
L100       26359 SEA FILE=BIOSIS ABB=ON  FIBRINOGEN?
L101       76395 SEA FILE=BIOSIS ABB=ON  ?ARTHRITI?
L102      806036 SEA FILE=BIOSIS ABB=ON  TUMOR? OR ?NEOPLAS? OR METASTAT?
L103       17987 SEA FILE=BIOSIS ABB=ON  ?RETINOPATH? OR MACULAR DEGENERATION
L104        4059 SEA FILE=BIOSIS ABB=ON  ?HISTOPLASM?
L105       18663 SEA FILE=BIOSIS ABB=ON  ?GLAUCOM?
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L106      33258 SEA FILE=BIOSIS ABB=ON  CORNEA?
L107       4531 SEA FILE=BIOSIS ABB=ON  ?KERATITI?
L108       3690 SEA FILE=BIOSIS ABB=ON  ?PTERYGI?
L109        667 SEA FILE=BIOSIS ABB=ON  PANNUS
L111        127 SEA FILE=BIOSIS ABB=ON  ALPHAVBETA5
L112       6987 SEA FILE=BIOSIS ABB=ON  NEOVASCUL?
L122         68 SEA FILE=WPIDS ABB=ON  L94 OR L111
L123       2223 SEA FILE=WPIDS ABB=ON  L93 OR L112
L126      31450 SEA FILE=WPIDS ABB=ON  (L100 OR L101 OR L102 OR L103 OR L104
                OR L105 OR L106 OR L107 OR L108 OR L109)
L127        476 SEA FILE=WPIDS ABB=ON  INTEGRIN#
L129     164755 SEA FILE=WPIDS ABB=ON  INHIBIT? OR ANTAGONI?
L130        236 SEA FILE=WPIDS ABB=ON  L127(8A)L129
L133      38851 SEA FILE=WPIDS ABB=ON  ?PEPTIDE?
L134          5 SEA FILE=WPIDS ABB=ON  L122 AND L123 AND L126 AND L130 AND
                L133

=> d que l137

L94         340 SEA FILE=BIOSIS ABB=ON  ALPHA(1W)BETA(W)5
L111        127 SEA FILE=BIOSIS ABB=ON  ALPHAVBETA5
L122         68 SEA FILE=WPIDS ABB=ON  L94 OR L111
L135        709 SEA FILE=WPIDS ABB=ON  METALLOPROTE?
L137          4 SEA FILE=WPIDS ABB=ON  L122 AND L135


=> s (l134 or l137) not l142

L155          6 (L134 OR L137) NOT (L142)  previously printed

=> dup rem l151, l153,l145,l152,l155

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PROCESSING COMPLETED FOR L145
PROCESSING COMPLETED FOR L152
PROCESSING COMPLETED FOR L155
L156         41 DUP REM L151 L153 L145 L152 L155 (6 DUPLICATES REMOVED)
                ANSWERS '1-10' FROM FILE MEDLINE
                ANSWERS '11-22' FROM FILE BIOSIS
                ANSWERS '23-32' FROM FILE CAPLUS
                ANSWERS '33-37' FROM FILE EMBASE
                ANSWERS '38-41' FROM FILE WPIDS

=> d ibib ab 1-41; fil hom
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DUPLICATE 3

L156 ANSWER 1 OF 41 MEDLINE
ACCESSION NUMBER: 2000166949 MEDLINE
DOCUMENT NUMBER: 20166949
TITLE: Molecular cloning and functional expression of contortrostatin, a homodimeric disintegrin from southern copperhead snake venom.
AUTHOR: Zhou Q; Hu P; Ritter M R; Swenson S D; Argounova S; Epstein A L; Markland F S
CORPORATE SOURCE: Department of Biochemistry, Norris Comprehensive Cancer Center, University of Southern California School of Medicine, Los Angeles, California, 90033, USA.
SOURCE: ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (2000 Mar 15) 375 (2) 278-88.
Journal code: 6SK. ISSN: 0003-9861.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200006
ENTRY WEEK: 20000603
AB Contortrostatin is a unique dimeric disintegrin isolated from southern copperhead snake venom. Through antagonism of integrins alphaIIbbeta3, alpha5beta1, alphavbeta3, and alphavbeta5, contortrostatin inhibits platelet aggregation and disrupts cancer cell adhesion and invasion. We cloned cDNA from a library made from the venom gland cells of Agkistrodon contortrix contortrix using polymerase chain reaction. We found that the contortrostatin gene is part of a precursor composed of proprotein, metalloproteinase, and disintegrin domains. The precursor cDNA is 2027 bp with a 1449-bp open reading frame. The disintegrin domain is 195 bp encoding 65 amino acids. Like other members of the disintegrin family, each subunit of contortrostatin has an RGD site, and the cysteine alignment is conserved. The disintegrin domain of the cDNA has been expressed in a eukaryotic expression system as a homodimeric fusion protein with an immunoglobulin. The recombinant protein is recognized by an antiserum against native contortrostatin in Western blot. Both the native and recombinant proteins bind to integrins alphavbeta3 and alphavbeta5. Like native contortrostatin, the recombinant fusion protein inhibits platelet aggregation, blocks cancer cell adhesion to fibronectin and vitronectin, and prevents invasion of cancer cells through a Matrigel barrier. The success of functional expression not only validates the cDNA cloning of this disintegrin, but also provides adequate material for functional studies of contortrostatin. Copyright 2000 Academic Press.

L156 ANSWER 2 OF 41 MEDLINE
ACCESSION NUMBER: 2000249065 MEDLINE
DOCUMENT NUMBER: 20249065
TITLE: Bone sialoprotein mediates human endothelial cell attachment and migration and promotes angiogenesis [see comments].
COMMENT: Comment in: Circ Res 2000 Apr 28;86(8):827-8
AUTHOR: Bellahc`ene A; Bonjean K; Fohr B; Fedarko N S; Robey F A; Young M F; Fisher L W; Castronovo V
CORPORATE SOURCE: Metastasis Research Laboratory, University of Li`ege, Li`ege, Belgium.
SOURCE: CIRCULATION RESEARCH, (2000 Apr 28) 86 (8) 885-91.
Journal code: DAJ. ISSN: 0009-7330.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY WEEK: 20000801
Searched by Barb O'Bryen, STIC 308-4291

AB Bone sialoprotein (BSP) is a secreted glycoprotein primarily found in sites of biomineralization. Recently, we demonstrated that BSP is strongly upregulated in osteotropic cancers and particularly those that exhibit microcalcifications. BSP contains an Arg-Gly-Asp (RGD) motif found in other adhesive molecules that interact with cellular integrins. In bone, BSP has been shown to mediate the attachment of osteoblasts and osteoclasts via alpha(v)beta(3) integrin receptors. Ligands for alpha(v)beta(3) integrin are considered to play a central role during angiogenesis. Therefore, we used human umbilical vein endothelial cells (HUVECs) to study the potential role of BSP in angiogenesis. We found that purified eukaryotic recombinant human BSP (rhBSP) is able to promote both adhesion and chemotactic migration of HUVECs in a dose-dependent manner. These interactions involve HUVEC alpha(v)beta(3) integrin receptors and the RGD domain of BSP. Indeed, HUVECs attach to a recombinant BSP fragment containing the RGD domain, whereas this response is not observed with the same fragment in which RGD has been mutated to Lys-Ala-Glu (KAE). A cyclic RGD BSP peptide inhibits both adhesion and migration of HUVECs to rhBSP. Moreover, anti-alpha(v)beta(3) but not anti-**alpha**(v)**beta** (**5**) monoclonal antibodies also prevent BSP-mediated adhesion and migration of HUVECs. We observed that both rhBSP and the RGD BSP recombinant fragment stimulated ongoing angiogenesis on the chorioallantoic chick membrane assay. BSP angiogenic activity was inhibited by anti-alpha(v)beta(3) antibody, and the KAE BSP fragment was inactive. Our findings represent the first report implicating BSP in angiogenesis. BSP could play a critical role in angiogenesis associated with bone formation and with tumor growth and metastatic dissemination.

L156 ANSWER 3 OF 41 MEDLINE
ACCESSION NUMBER: 2000208934 MEDLINE
DOCUMENT NUMBER: 20208934
TITLE: In vitro and in vivo effects of a cyclic peptide with affinity for the alpha(nu)beta3 integrin in human melanoma cells.
AUTHOR: Allman R; Cowburn P; Mason M
CORPORATE SOURCE: Research Department, Velindre Hospital, Whitchurch, Cardiff, UK.
SOURCE: EUROPEAN JOURNAL OF CANCER, (2000 Feb) 36 (3) 410-22. Journal code: ARV. ISSN: 0959-8049.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200006
ENTRY WEEK: 20000604

AB Expression of the integrin alpha(nu)beta3 has been shown to be associated with increasing metastatic potential in malignant melanoma. It also has a functional role on vascular endothelial cells during angiogenesis. The cyclic oligopeptide cRGDfV is known to bind with high affinity to alpha(nu)beta3. We have investigated the cellular effects of cRGDfV on a panel of human melanoma cell lines in vitro and also on the A375 melanoma cell line growing as xenografts in nude mice. cRGDfV is a potent inhibitor of alpha(nu)beta3-mediated cell adhesion, however, we have found no convincing evidence that integrin ligation by cRGDfV induces apoptosis in melanoma cell lines. However, cRGDfV when administered subcutaneously into nude mice did inhibit the growth of A375 melanoma xenografts. Histological examination of the tumours indicated that this effect was primarily one of angiogenesis inhibition. The results suggest that agents which target the alpha(nu)beta3 integrin may have a useful role as anti-angiogenesis agents in clinical oncology, but that they may not exert a direct effect on alphavbeta3-expressing tumour cells.

L156 ANSWER 4 OF 41 MEDLINE

ACCESSION NUMBER: 2000349400 MEDLINE
DOCUMENT NUMBER: 20349400
TITLE: Shear stress downregulation of platelet-derived growth factor receptor-beta and matrix metalloprotease-2 is associated with inhibition of smooth muscle cell invasion and migration.
AUTHOR: Palumbo R; Gaetano C; Melillo G; Toschi E; Remuzzi A; Capogrossi M C
CORPORATE SOURCE: Laboratorio di Patologia Vascolare, Istituto Dermopatico dell'Immacolata, Istituto di Ricovero e Cura a Carattere Scientifico, Rome, Italy.
SOURCE: CIRCULATION, (2000 Jul 11) 102 (2) 225-30.
Journal code: DAW. ISSN: 0009-7322.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200010
ENTRY WEEK: 20001001
AB BACKGROUND: After endovascular injury, smooth muscle cells (SMCs) may be exposed to hemodynamic shear stress (SS), and these forces modulate neointima accumulation. The effect of SS on SMC migration and invasion is unknown, and it was examined in the present study. METHODS AND RESULTS: Bovine aortic SMCs were exposed to laminar SS of 12 dyne/cm(2) for 3 (SS3) or 15 (SS15) hours; control (C3 and C15) SMCs were kept under static conditions. Platelet-derived growth factor (PDGF)-BB-directed SMC migration and invasion were evaluated by a modified Boyden chamber assay with filters coated with either gelatin or reconstituted basement membrane proteins (Matrigel), respectively. SS15 inhibited both SMC migration and invasion ($P<0.0001$). There was no significant difference between SS3 and C3 cells. Media conditioned with SS15 cells exhibited a reduction in matrix metalloprotease-2 (MMP-2) by zymography and Western analysis. Northern blot analysis revealed no effect of SS15 on MMP-2 mRNA. In contrast, SS15 decreased MMP-2 activator and membrane-type MMP (MT-MMP or MMP-14) mRNA and protein. Furthermore, SS15 decreased PDGF receptor-beta (PDGF-Rbeta) mRNA and protein ($P<0.05$), and the SS-dependent decrease in PDGF-BB-directed cell migration was rescued by overexpressing PDGF-Rbeta. CONCLUSIONS: SS inhibits SMC migration and invasion via diminished PDGF-Rbeta expression. This effect of SS is associated with decreased MMP-2 secretion and MT-MMP downregulation.

L156 ANSWER 5 OF 41 MEDLINE
ACCESSION NUMBER: 1999196136 MEDLINE
DOCUMENT NUMBER: 99196136
TITLE: Insulin-like growth factor I-triggered cell migration and invasion are mediated by matrix metalloproteinase-9.
AUTHOR: Mira E; Manes S; Lacalle R A; Marquez G; Martinez-A C
CORPORATE SOURCE: Department of Immunology and Oncology, Centro Nacional de Biotecnologia, Consejo Superior de Investigaciones Cientificas, Universidad Autonoma de Madrid, Spain.. emira@cnb.uam.es
SOURCE: ENDOCRINOLOGY, (1999 Apr) 140 (4) 1657-64.
Journal code: EGZ. ISSN: 0013-7227.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199906
AB MCF-7 cells migrate through vitronectin-coated filters in response to insulin-like growth factor I (IGF-I); migration is inhibited by the matrix metalloproteinase (MMP) inhibitor BB-94, but not by the serine proteinase

inhibitor aprotinin. MMP-9 was identified in the conditioned medium of MCF-7 cells; in addition, fluorescence-activated cell sorting analysis revealed its presence on the cell surface, where MMP-9 activity was also found using a specific fluorogenic peptide. Furthermore, the messenger RNA encoding MMP-9 was detected in MCF-7 cells by PCR. The IGF-I concentration leading to maximal MCF-7 invasion produces an increase in cell surface proteolytic activity after short incubation periods. At 18 h, however, preincubation of MCF-7 cells with IGF-I produces at 18 h a dose-dependent decrease in cell-associated MMP-9 activity and an increase in soluble MMP-9. MCF-7 invasion is dependent on the alpha(v)beta5 integrin, a vitronectin receptor. The levels of alpha(v)- and beta5-subunits expressed in MCF-7 cells depend on the IGF-I concentration, which triggers an increase in both of these subunits. Based on these results, we suggest that IGF-I-induced MCF-7 cell migration is mediated by the MMP-9 activity on the cell surface and by alpha(v)beta5 integrin.

L156 ANSWER 6 OF 41 MEDLINE
ACCESSION NUMBER: 1999156363 MEDLINE
DOCUMENT NUMBER: 99156363
TITLE: ETS-1 converts endothelial cells to the angiogenic phenotype by inducing the expression of matrix metalloproteinases and integrin beta3.
AUTHOR: Oda N; Abe M; Sato Y
CORPORATE SOURCE: Department of Vascular Biology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan.
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (1999 Feb) 178 (2) 121-32. Journal code: HNB. ISSN: 0021-9541.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199905
AB The transcription factor ETS-1 is induced in endothelial cells (ECs) by angiogenic growth factors and the specific elimination of ETS-1 synthesis by antisense oligodeoxynucleotide inhibited angiogenesis in vitro (Iwasaka et al., 1996, J Cell Physiol 169:522-531). To understand the precise role of ETS-1 in angiogenesis, we established both high and low ETS-1 expression EC lines and compared angiogenic properties of these cell lines with those of the parental murine EC line, MSS-31. Although growth rate was almost identical for each cell line, the invasiveness was markedly enhanced in high ETS-1 expression cells and reduced in low ETS-1 expression cells compared with that of parental cells. The gene expressions of matrix metalloproteinases (MMP-1, MMP-3, and MMP-9) and gelatinolytic activity of MMP-9 were significantly increased in high ETS-1 expression cells. Low ETS-1 expression cells could not spread on a vitronectin substratum, and the phosphorylation of focal adhesion kinase was markedly impaired because of the reduced expression of integrin beta3. These results indicate that ETS-1 is a principal regulator that converts ECs to the angiogenic phenotype.

L156 ANSWER 7 OF 41 MEDLINE
ACCESSION NUMBER: 1998196361 MEDLINE
DOCUMENT NUMBER: 98196361
TITLE: Selective alpha v beta 3 integrin blockade potently limits neointimal hyperplasia and lumen stenosis following deep coronary arterial stent injury: evidence for the functional importance of integrin alpha v beta 3 and osteopontin expression during neointima formation.
AUTHOR: Srivatsa S S; Fitzpatrick L A; Tsao P W; Reilly T M; Holmes D R Jr; Schwartz R S; Mousa S A
CORPORATE SOURCE: Department of Internal Medicine, Mayo Clinic, Rochester, MN 55905, USA.

Searched by Barb O'Bryen, STIC 308-4291

CONTRACT NUMBER: NHLB 51736
SOURCE: CARDIOVASCULAR RESEARCH, (1997 Dec) 36 (3) 408-28.
Journal code: COR. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY WEEK: 19980701

AB Lumen loss from vascular restenosis remains a leading cause of chronic revascularization failure. OBJECTIVE: We hypothesized that cell-matrix adhesion, migration, and differentiation events that underlie restenosis are mediated by alpha v beta 3 integrin-ligand interactions. METHODS: Using immunohistochemistry and in situ hybridization, we examined the spatial and temporal vessel wall expression of alpha v beta 3 and osteopontin following deep coronary arterial injury. Cell migration and adhesion assays were performed to demonstrate the affinity and specificity of XJ 735 for various vessel wall integrins. The effects of XJ 735 (a selective cyclic Arg-Gly-Asp (RGD) peptidomimetic alpha v beta 3 antagonist) on neointimal hyperplasia and lumen stenosis were tested in a porcine coronary injury model. Normolipemic swine underwent oversized stent injury followed by XJ 735 administration (9 animals, 28 lesions; 1 mg/kg bolus + 7 days 4 mg/kg/d infusion + 21 days 2 mg/kg i.v. bolus 12 hourly) or placebo (10 animals, 30 arterial lesions). RESULTS: Maximal alpha v beta 3 immunoreactivity was observed between 7-14 days following injury in the neointima, media, and adventitia. Maximal osteopontin mRNA signal in the neointima, media, and adventitia was observed at 14, 7 and 28 days respectively. IC50 for XJ 735 alpha v beta 3-mediated inhibition of human and porcine endothelial cell adhesion, and vascular smooth muscle cell migration, ranged from 0.6 to 4.4 microM. In contrast, IC50 for porcine or human alpha IIb/beta 3, alpha 4 beta 1, **alpha** v **beta 5**, and alpha 5 beta 1 inhibition exceeded 100 microM. Steady state XJ 735 plasma levels exceeded 5 microM. Despite slightly higher injury scores in XJ 735 treated animals, significant reductions in mean neointima area (43% reduction; $p = 0.0009$), and mean percent lumen stenosis (approximately 2.9 fold reduction; $p = 0.04$) were observed in XJ 735 treated animals. XJ 735 treatment did not significantly alter the relative size of the arterial injury and reference sites (geometric remodeling). Comparison of neontima area vs. injury score regression lines revealed significant reductions in slope ($p = 0.0001$) and intercept ($p = 0.0001$) for XJ 735. CONCLUSIONS: Selective alpha v beta 3 blockade is an effective anti-restenosis strategy that potently limits neointimal growth and lumen stenosis following deep arterial injury. The co-ordinate spatial and temporal upregulation of alpha v beta 3 expression following vessel wall injury, and the high affinity and specificity of XJ 735 for alpha v beta 3, confirms the importance of this integrin in adhesive and migratory cell-matrix events underlying coronary restenosis.

L156 ANSWER 8 OF 41 MEDLINE
ACCESSION NUMBER: 97155528 MEDLINE
DOCUMENT NUMBER: 97155528
TITLE: The role of vascular cell integrins alpha v beta 3 and **alpha** v **beta 5** in angiogenesis.
AUTHOR: Varner J A
CORPORATE SOURCE: Department of Medicine, University of California, San Diego, La Jolla 92093-0063, USA.
SOURCE: EXS, (1997) 79 361-90. Ref: 243
Journal code: BFZ.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
Searched by Barb O'Bryen, STIC 308-4291

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY WEEK: 19970404

L156 ANSWER 9 OF 41 MEDLINE
ACCESSION NUMBER: 97050414 MEDLINE
DOCUMENT NUMBER: 97050414
TITLE: Altered integrin expression in rheumatoid synovial lining type B cells: in vitro cytokine regulation of alpha 1 beta 1, alpha 6 beta 1, and **alpha** v **beta** **5** integrins.
AUTHOR: Pirila L; Heino J
CORPORATE SOURCE: Department of Medical Biochemistry, MediCity Research Laboratory, University of Turku, Finland.
SOURCE: JOURNAL OF RHEUMATOLOGY, (1996 Oct) 23 (10) 1691-8. Journal code: JWX. ISSN: 0315-162X.
PUB. COUNTRY: Canada
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
AB OBJECTIVE: We recently showed that in rheumatoid arthritis (RA) the extracellular matrix around the lining cells is similar to the matrix seen in osteoarthritis, whereas the cellular adhesion apparatus is very different. In hyperplastic synovial membrane there is very little of alpha 6, alpha v, and beta 5 integrin subunits, whereas in noninflammatory synovial membrane these integrins are well expressed. We studied how expression of these cell adhesion molecules is regulated in RA in vitro. METHODS: The integrin expression in 6 different synovial fibroblast strains representing the type B cells and in THP-1 cell line was examined by immunoprecipitation, flow cytometry, and Northern hybridization. RESULTS: Proinflammatory cytokines, especially interleukin 1 beta, increased the expression of alpha 1 integrin in synovial fibroblasts. When the monocyte-like THP-1 cells were induced to differentiate to adherent macrophages they started to express alpha 6 and beta 5 integrin subunits. In adherent THP-1 cells the expression of integrin alpha 6 subunit was strongly enhanced by transforming growth factor-beta and downregulated by the combination of tumor necrosis factor-alpha and interferon-gamma. CONCLUSION: Cytokines regulate the cell adhesion molecules of synovial fibroblasts and mononuclear phagocytes in vitro causing alterations in integrin expression similar to the ones seen in rheumatoid synovium in vivo.

L156 ANSWER 10 OF 41 MEDLINE
ACCESSION NUMBER: 1998298508 MEDLINE
DOCUMENT NUMBER: 98298508
TITLE: Phage libraries displaying cyclic peptides with different ring sizes: ligand specificities of the RGD-directed integrins.
AUTHOR: Koivunen E; Wang B; Ruoslahti E
CORPORATE SOURCE: Cancer Research Center, La Jolla Cancer Research Foundation, CA 92037, USA.
CONTRACT NUMBER: CA42507 (NCI)
CA28896 (NCI)
CA30199 (NCI)
SOURCE: BIO/TECHNOLOGY, (1995 Mar) 13 (3) 265-70. Journal code: AL1. ISSN: 0733-222X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; B

ENTRY MONTH: 199809
ENTRY WEEK: 19980904
AB We have isolated selective ligands to the cell surface receptors of fibronectin (alpha 5 beta 1 integrin), vitronectin (alpha v beta 3 and **alpha** v **beta 5** integrins) and fibrinogen (alpha IIb beta 3 integrin) from phage libraries expressing cyclic peptides. A mixture of libraries was used that express a series of peptides flanked by a cysteine residue on each side (CX5C, CX6C, CX7C) or only on one side (CX9) of the insert. A majority of the integrin-binding sequences derived from the CX9 library contained another cysteine, indicating preferential selection of conformationally constrained cyclic peptides. Each of the four integrins studied primarily selected RGD-containing phage sequences but favored different ring sizes and different flanking residues around the RGD motif. A cyclic peptide ACRGDGWCG was synthesized based on a phage sequence that bound particularly avidly to the alpha 5 beta 1 integrin. This peptide inhibited cell attachment to fibronectin at about 5-fold lower concentrations than the most potent cyclic peptides described earlier. The most interesting structure appeared to contain two disulphide bonds. One such peptide, ACDCRGDCFCG, was synthetized and shown to be at least 20-fold more potent inhibitor of **alpha** v **beta 5**- and alpha v beta 3-mediated cell attachment to vitronectin than similar peptides with a single disulphide bond and 200-fold more potent than commonly used linear RGD peptides. These results emphasize the importance of conformational restriction as a means of improving the potency of integrin-binding peptides and point to a new way of designing effective peptides by resticting the peptide conformation with more than one cyclizing bond.

L156 ANSWER 11 OF 41 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 4
ACCESSION NUMBER: 1999:318913 BIOSIS
DOCUMENT NUMBER: PREV199900318913
TITLE: Novel small molecule alphav **integrin** **antagonists**: Comparative anti-cancer efficacy with known **angiogenesis inhibitors**.
AUTHOR(S): Kerr, Janet S. (1); Wexler, Roseanne S.; Mousa, Shaker A.; Robinson, Candy S.; Wexler, Eric J.; Mohamed, Seema; Voss, Matthew E.; Devenny, James J.; Czerniak, Philip M.; Gudzelak, Andrew, Jr.; Slee, Andrew M.
CORPORATE SOURCE: (1) Experimental Station E400/4223, DuPont Pharmaceuticals Co., Wilmington, DE, 19880-0400 USA
SOURCE: Anticancer Research, (March-April, 1999) Vol. 19, No. 2A, pp. 959-968.
ISSN: 0250-7005.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Recent evidence supports the involvement of integrins in **angiogenesis**: blockade of alphavbeta3 and **alphavbeta5** integrins disrupts **angiogenesis** leading to decreased blood vessel formation and hence decreased **tumor** growth. We hypothesized that av antagonists could **inhibit tumor** growth in **tumor** cells devoid of alphavbeta3 **integrins**. We evaluated SM256 and SD983, novel small molecules that are specific av antagonists in mouse models of **angiogenesis** and **tumorigenesis**, and compared them with standards: TNP470, a fumagillin analog in the clinic, and flavopiridol, a cell cycle kinase inhibitor. In vitro SM256 was a selective alphavbeta3 inhibitor with an IC50=4nM, and the affinity of SD983 against the mouse endothelial alphavbeta3 integrin yielded an IC50=2nM and an IC50=54nM against **alphavbeta5**. In the mouse Matrigel model of **angiogenesis** SM256 decreased blood vessel formation (hemoglobin content) with an

ED50=0.055 ug/kg/day, tenfold more potent than TNP470. SG545, an ester of SD983, decreased blood vessel formation with an ED50=6 ug/kg/day, while flavopiridol ED50=18 ug/kg/day. In the mouse xenograft model, using human colon carcinoma RKO cells that do not express alphavbeta3 but express **alphavbeta5**, **tumor** growth was inhibited by SG545 (10 mg/kg/day) and flavopiridol (5 mg/kg/every other day) 40% and 70%, respectively ($p < 0.05$). Although the proliferative index (measured by BrdU incorporation) was not significantly changed with SM256, SG545 or flavopiridol (29-32%), the apoptotic index increased significantly ($p < 0.05$) in the SM256 and SG545-treated groups (2.3-2.7%) compared with controls (1.1%), suggesting increased cell death contributed to decreased **tumor** volumes. **Neovascularization** decreased with SM256 and SG545 treatment. The data demonstrate that potent selective av antagonists can target endothelial cells, **tumor** cells, inhibit **angiogenesis** and inhibit **tumor** growth.

L156 ANSWER 12 OF 41 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 5
ACCESSION NUMBER: 1998:207242 BIOSIS
DOCUMENT NUMBER: PREV199800207242
TITLE: Vitronectin decreases microvascular endothelial cell apoptosis.
AUTHOR(S): Isik, F. Frank (1); Gibran, Nicole S.; Jang, Young-Chul; Sandell, Linda; Schwartz, Stephen M.
CORPORATE SOURCE: (1) Dep. Surg., 112 VA Med. Cent., 1660 S. Columbian Way, Seattle, WA 98108 USA
SOURCE: Journal of Cellular Physiology, (May, 1998) Vol. 175, No. 2, pp. 149-155.
ISSN: 0021-9541.
DOCUMENT TYPE: Article
LANGUAGE: English
AB **Angiogenesis** after tissue injury occurs in a matrix environment consisting of fibrin, fibronectin, and vitronectin as the major extracellular matrix (ECM) constituents. ECM-integrin interactions is critical for **angiogenesis** and failure to bind a ligand to certain **integrin** receptors (alphavbeta3 or **alphavbeta5**) **inhibits angiogenesis**. The ligand that binds to alphavbeta3 or **alphavbeta5** integrin receptors during microvascular **angiogenesis** has not been identified. Our hypothesis is that provisional matrix molecules provide the environmental context cues to microvascular endothelial cells and promote **angiogenesis** by decreased programmed cell death. Using cultured human microvascular endothelial cells, we show that vitronectin, in comparison to growth on alternative provisional matrix molecules (fibronectin, **fibrinogen** plus thrombin), collagen I, and basement membrane molecules (collagen IV), significantly reduces microvascular endothelial cell death in vitro. This reduction was observed using morphologic criteria, TdT-mediated dUTP nick end labeling (TUNEL) assay, histone release into the cytoplasm, and thymidine release into the supernatant. Though our data confirm that vitronectin may bind to more than one integrin receptor to reduce MEC apoptosis, binding to the alphav component appears to be the critical integrin subcomponent for reducing apoptosis.

L156 ANSWER 13 OF 41 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:341699 BIOSIS
DOCUMENT NUMBER: PREV200000341699
TITLE: **Integrin** receptor **antagonists**.
AUTHOR(S): Askew, Ben C. (1); Coleman, Paul J.; Duggan, Mark E.; Halczenko, Wasyl; Hutchinson, John H.; Meissner, Robert S.; Patane, Michael A.; Wang, Jiabing
CORPORATE SOURCE: (1) Lansdale, PA USA
ASSIGNEE: Merck & Co., Inc.

PATENT INFORMATION: US 6017926 January 25, 2000
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Jan. 25, 2000) Vol. 1230, No. 4, pp. No pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB The present invention relates to compounds and derivatives thereof, their synthesis, and their use as **integrin** receptor **antagonists**. More particularly, the compounds of the present invention are **antagonists** of the **integrin** receptors alphavbeta3, **alphavbeta5** and/or alphavbeta6 and are useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting vascular restenosis, diabetic **retinopathy**, **macular degeneration**, **angiogenesis**, atherosclerosis, inflammation, wound healing, viral disease, and **tumor** growth and metastasis.

L156 ANSWER 14 OF 41 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:341698 BIOSIS
DOCUMENT NUMBER: PREV200000341698
TITLE: **Integrin antagonists.**
AUTHOR(S): Duggan, Mark E. (1)
CORPORATE SOURCE: (1) Schwenksville, PA USA
ASSIGNEE: Merck & Co., Inc.
PATENT INFORMATION: US 6017925 January 25, 2000
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Jan. 25, 2000) Vol. 1230, No. 4, pp. No pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB This invention relates to certain novel compounds and derivatives thereof, their synthesis, and their use as vitronectin receptor antagonists. The vitronectin receptor antagonist compounds of the present invention are alphavbeta3 antagonists, **alphavbeta5** antagonists or dual alphavbeta3/**alphavbeta5** antagonists useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting restenosis, diabetic **retinopathy**, **macular degeneration**, **angiogenesis**, atherosclerosis, inflammation, viral disease, and **tumor** growth.

L156 ANSWER 15 OF 41 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:310522 BIOSIS
DOCUMENT NUMBER: PREV200000310522
TITLE: Effects of the novel alphav **integrin** **antagonist** SM256 and cis-platinum on growth of murine squamous cell carcinoma PAM LY8.
AUTHOR(S): van Waes, Carter (1); Enamorado-Ayala, Ileana; Hecht, David; Sulica, Lucien; Chen, Zhong; Batt, Douglas G.; Mousa, Shaker
CORPORATE SOURCE: (1) Tumor Biology Section, Head and Neck Surgery Branch, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bldg. 10, Rm. 5D55, Bethesda, MD, 20892-1419 USA
SOURCE: International Journal of Oncology, (June, 2000) Vol. 16, No. 6, pp. 1189-1195. print.
ISSN: 1019-6439.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Increased density of proliferating and migrating **tumor** cells and

neovascular endothelial cells has been associated with **tumor** progression and poor prognosis in patients with squamous cell carcinoma (SCC). **Tumor** and **neovascular** endothelial cells in squamous cell carcinoma have been reported to express integrin heterodimers containing the av subunit, which binds to vitronectin and other extra-cellular matrix proteins that contain the amino acid recognition sequence Arg-Gly-Asp (RGD). In the present study, we examined the effect of the novel non-peptide av **integrin antagonist** 5M256 on growth of SCC line PAM LY8 in BALB/c SCID mice, and determined whether SM256 has direct inhibitory effects on growth of murine endothelial and PAM LY8 SCC cells in vitro. SM256 inhibits cell adhesion of murine cells expressing alphavbeta3 and **alphavbeta5** integrins in vitro with an IC50 of 35 nM and 30 nM, respectively. Growth of PAM LY8 **tumors** in vivo was inhibited with 14-day continuous administration of SM256 by subcutaneous osmotic diffusion pump, during which a mean serum concentration of 56 nM was detected. While both murine aortic endothelial cells and PAM LY8 were found to express alphav integrins by fluorescence cytofluorometry, SM256 at 50 nM in MTT assay completely inhibited growth of endothelial cells, but had no significant direct effect on growth of PAM LY8 cells. We compared the effect on growth of PAM LY8 of SM256 infusion versus single agent or combination chemotherapy with a maximally tolerated dose of cis-platinum, which is used as a standard chemotherapy for SCC. When treatment was initiated at either 7 or 21 days following establishment of **tumor**, 14-day infusion of SM256 had an inhibitory effect on growth that was similar to that obtained with single dose cis-platinurn, but no additive effect of concurrent therapy with SM256 and cis-platinum was observed. These results demonstrate the activity and feasibility of use of alphav antagonists such as SM256 for therapy of SCC.

L156 ANSWER 16 OF 41 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:275619 BIOSIS
DOCUMENT NUMBER: PREV200000275619
TITLE: Contortrostatin (CN), a dimeric disintegrin **inhibits** invasion of ovarian cancer by blocking **integrin alphavbeta5**.
AUTHOR(S): Zhou, Qing (1); Shieh, Kate Y. (1); Markland, Francis S. (1)
CORPORATE SOURCE: (1) Univ of Southern CA, Los Angeles, CA USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 800. print.. Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L156 ANSWER 17 OF 41 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:122111 BIOSIS
DOCUMENT NUMBER: PREV200000122111
TITLE: Integrins alphavbeta3 and **alphavbeta5** are expressed by endothelium of high-risk neuroblastoma and their inhibition is associated with increased endogenous ceramide.
AUTHOR(S): Erdreich-Epstein, Anat; Shimada, Hiroyuki; Groshen, Susan; Liu, Ming; Metelitsa, Leonid S.; Kim, Kwang Sik; Stins, Monique F.; Seeger, Robert C.; Durden, Donald L. (1)
CORPORATE SOURCE: (1) Department of Pediatrics, Herman B. Wells Center for Pediatric Research, Cancer Research Institute, Indiana University School of Medicine, 1044 West Walnut Street,

Room 468, Indianapolis, IN, 46202 USA
SOURCE: Cancer Research, (Feb. 1, 2000) Vol. 60, No. 3, pp. 712-721.
ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Inhibition** of the RGD-binding **integrins**, alphavbeta3 and **alphavbeta5**, prevents endothelial cell anchorage and induces endothelial apoptosis, which results in disruption of **tumor angiogenesis** and inhibition of **tumor** growth in animal models. In this study, we demonstrate by immunohistochemical analysis that integrin alphavbeta3 was expressed by 61% (mean) of microvessels in high-risk neuroblastomas (stage IV and MYCN-amplified stage III; n = 28) but only by 18% (mean) of microvessels in low-risk **tumors** (stages I and II and non-MYCN-amplified stage III; n = 12). Integrin **alphavbeta5** was found on 60% (mean) of microvessels in 21 Stage IV **tumors**. These data suggest that neuroblastomas may be targeted for **antiangiogenic** treatment directed against endothelial **integrins** alphavbeta3 and **alphavbeta5**. In cell culture, **inhibition** of **integrin**-dependent endothelial cell anchorage to vitronectin by RGDfV, an RGD function-blocking cyclic peptide, induced apoptosis in bovine brain endothelial cells compared with the control peptide, RADfV (37.5% versus 8.7%, respectively), as detected by chromatin condensation and nuclear fragmentation. Treatment with RGDfV but not with RADfV, which prevented attachment of endothelial cells to vitronectin or fibronectin, was associated with up to a 50% increase in endogenous ceramide, a lipid second messenger that can mediate cell death. Furthermore, exogenous C2-ceramide was cytotoxic to bovine brain endothelial cells and induced activation of C-jun N-terminal kinase (JNK), a MAP kinase that can be activated in stress-induced apoptosis pathways. This suggests that ceramide may function in detachment-induced endothelial cell apoptosis, originating from **inhibition** of vitronectin binding to **integrins** such as alphavbeta3 and **alphavbeta5** . This is the first report to demonstrate expression of integrins alphavbeta3 and **alphavbeta5** by microvascular endothelium of a childhood **tumor** and association of their expression with neuroblastoma aggressiveness. Furthermore, our data provide the first suggestion that inhibition of endothelial cell anchorage, resulting from specific blockade of RGD-binding integrins, increases endogenous ceramide, which may contribute to endothelial cell death.

L156 ANSWER 18 OF 41 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:366936 BIOSIS
DOCUMENT NUMBER: PREV200000366936
TITLE: Phase I and pharmacologic study of EMD 121974, an alpha,beta3 and alpha,beta5 **integrin** **inhibitor** that pertubs **tumor** **angiogenesis**, in patients with solid **tumors** .

AUTHOR(S): Eskens, F. (1); Dumez, H.; Verweij, J.; Perschl, A.; Kovar, A.; Brindley, C.; van Oosterom, A.
CORPORATE SOURCE: (1) Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital Rotterdam, Rotterdam Netherlands

SOURCE: Annals of Hematology, (2000) Vol. 79, No. Suppl. 2, pp. S2. print.
Meeting Info.: Transplantation in Hematology and Oncology II: From Novel Strategies to Clinical Trials Muenster, Germany April 09-11, 2000
ISSN: 0939-5555.
DOCUMENT TYPE: Conference
LANGUAGE: English

SUMMARY LANGUAGE: English

L156 ANSWER 19 OF 41 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:290335 BIOSIS
DOCUMENT NUMBER: PREV200000290335
TITLE: **Integrin antagonists.**
AUTHOR(S): Duggan, Mark E. (1); Hartman, George D.; Hoffman, William F.; Meissner, Robert S.; Perkins, James J.; Askew, Ben C.; Coleman, Paul J.; Hutchinson, John H.; Naylor-Olsen, Adel M.
CORPORATE SOURCE: (1) Lansdale, PA USA
ASSIGNEE: Merck & Co., Inc., Rahway, NJ, USA
PATENT INFORMATION: US 5981546 November 09, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 9, 1999) Vol. 1228, No. 2, pp. No pagination. e-file..
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB This invention relates to certain novel compounds and derivatives thereof, their synthesis, and their use as vitronectin receptor antagonists. The vitronectin receptor antagonist compounds of the present invention are alphavbeta3 antagonists, **alphavbeta5** antagonists or dual alphavbeta3/**alphavbeta5** antagonists useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting restenosis, diabetic **retinopathy**, **macular degeneration**, **angiogenesis**, atherosclerosis, inflammation and **tumor** growth.

L156 ANSWER 20 OF 41 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:243120 BIOSIS
DOCUMENT NUMBER: PREV199800243120
TITLE: Systemically administered peptide **antagonists** of alphavbeta3 and **alphavbeta5 integrins** **inhibit** cytokine-stimulated rabbit **corneal** **neovascularization**.
AUTHOR(S): Aguilar, H. E.; Friedlander, M.
CORPORATE SOURCE: Dep. Cell Biol., Scripps Res. Inst., La Jolla, CA USA
SOURCE: IOVS, (March 15, 1998) Vol. 39, No. 4, pp. S895.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA May 10-15, 1998 Association for Research in Vision and Ophthalmology
.
DOCUMENT TYPE: Conference
LANGUAGE: English

L156 ANSWER 21 OF 41 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1999:17392 BIOSIS
DOCUMENT NUMBER: PREV199900017392
TITLE: The molecular and cellular biology of pancreatic cancer.
AUTHOR(S): Perugini, Richard A.; McDade, Theodore P.; Vittimberga, Frank J., Jr.; Callery, Mark P. (1)
CORPORATE SOURCE: (1) Division General Surgery, University Massachusetts-Memorial Health System, 55 Lake Avenue North, Worcester, MA 01655-3333 USA
SOURCE: Critical Reviews in Eukaryotic Gene Expression, (1998) Vol. 8, No. 3-4, pp. 377-393.
ISSN: 1045-4403.
DOCUMENT TYPE: Article
LANGUAGE: English

L156 ANSWER 22 OF 41 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:349305 BIOSIS
DOCUMENT NUMBER: PREV199800349305
TITLE: Tissue remodeling in cancer and anti-cancer therapy.
AUTHOR(S): Van Waes, Carter; Hecht, David A.; Mousa, Shaker A. (1)
CORPORATE SOURCE: (1) Du Pont Merck Pharm. Corp., Exp. Stn. E400/3456, Wilmington, DE 19880-0400 USA
SOURCE: Biochemical Archives, (May, 1998) Vol. 14, No. 2, pp. 71-91.
ISSN: 0749-5331.
DOCUMENT TYPE: Article
LANGUAGE: English

L156 ANSWER 23 OF 41 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 1
ACCESSION NUMBER: 2000:535017 CAPLUS
DOCUMENT NUMBER: 133:155403
TITLE: **Integrin antagonists** for **inhibiting** brain **tumor** growth
INVENTOR(S): Laug, Walter E.
PATENT ASSIGNEE(S): Childrens Hospital Los Angeles, USA
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000044404	A2	20000803	WO 2000-US1949	20000126

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-118126 19990201
US 2000-489391 20000121

AB The present invention describes methods for inhibition of **tumor** growth in the brain, using antagonists of integrins such as .alpha.v.beta.3 and **.alpha.v.beta.5**. Antagonists of the present invention can inhibit **angiogenesis** in brain **tumor** tissue. They can also inhibit vitronectin and tenascin-mediated cell adhesion and migration in brain **tumor** cells. They can further induce direct brain **tumor** cell death.

L156 ANSWER 24 OF 41 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 2
ACCESSION NUMBER: 2000:411022 CAPLUS
DOCUMENT NUMBER: 133:129427
TITLE: Small molecule .alpha.v **integrin** **antagonists**: novel anticancer agents
AUTHOR(S): Kerr, Janet S.; Slee, Andrew M.; Mousa, Shaker A.
CORPORATE SOURCE: General Pharmacology, DuPont Pharmaceuticals Co., Wilmington, DE, 19880-0400, USA
SOURCE: Expert Opin. Invest. Drugs (2000), 9(6), 1271-1279
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
Searched by Barb O'Bryen, STIC 308-4291

AB A review with 112 refs. The members of the integrin family are targets that potentially provide both therapeutic and diagnostic opportunities. Advances in the understanding of the signaling pathways, transcriptional regulation and the structure/function relationships of the adhesion mols. to extracellular matrix proteins have all contributed to these opportunities. The role of the integrins in pathol. processes in both acute and chronic diseases, include ocular, cancer (solid **tumors** and metastasis), cardiovascular (stroke and heart failure) and inflammatory (rheumatoid **arthritis**) conditions. Various therapeutic candidates, including antibodies, cyclic peptides and peptidomimetics, have been identified. This review will focus on the key role of the .alpha.v integrin (.alpha.v.beta.3 and .**alpha**.**v**.**beta**.**5**) in **angiogenic** processes in **tumors**, including its potential use in cancer diagnostics and therapy.

REFERENCE COUNT: 112
REFERENCE(S): (1) Agrez, M; Cell Biol 1994, V127, P547 CAPLUS
(2) Albelda, S; Cancer Res 1990, V50, P6757 CAPLUS
(4) Allman, R; Eur J Cancer 2000, V36, P410 CAPLUS
(6) Arap, W; Science 1998, V279, P377 CAPLUS
(7) Bach, A; J Am Chem Soc 1996, V118, P293 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L156 ANSWER 25 OF 41 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 6
ACCESSION NUMBER: 1997:740435 CAPLUS
DOCUMENT NUMBER: 128:39550
TITLE: Combinations of **angiostatic** compounds
INVENTOR(S): Doshi, Rupa; Clark, Abbot F.
PATENT ASSIGNEE(S): Clark, Abbot F., USA; Doshi, Rupa; Alcon Laboratories, Inc.
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9741844	A1	19971113	WO 1997-US5574	19970403
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9724382	A1	19971126	AU 1997-24382	19970403
PRIORITY APPLN. INFO.:			US 1996-17096	19960509
			WO 1997-US5574	19970403

OTHER SOURCE(S): MARPAT 128:39550
AB The present invention is directed to compns. contg. combinations of **angiostatic** compds. (chromans or benzofurans and e.g., steroids) and methods for their use in preventing pathol. neovascularization. Thus, 2-(5-hydroxy-2,4,6,7-tetramethyl-3,4-dihydrobenzo[1,2-b]furan-2-yl)ethyl 2-(6-methoxy-2-naphthyl)propionate (I) was prepd. by the reaction of 2-(5-hydroxy-2,4,6,7-tetramethyl-3,4-dihydrobenzo[1,2-b]furan-2-yl)ethanol with 6-methoxy-.alpha.-methylnaphthaleneacetic acid in the presence of dimethylaminopyridine and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide-HCl in THF. Thus, a topical ocular soln. contained I 1.0, another **angiostatic** compd.0.005-5.0%, benzalkonium chloride 0.01, HPMC 0.5, NaCl 0.8, Na phosphate 0.28, and disodium edetate 0.01%, NaOH/HCl qs pH 7.2, and water qs to 100 mL.

L156 ANSWER 26 OF 41 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:592698 CAPLUS
DOCUMENT NUMBER: 133:164332
Searched by Barb O'Bryen, STIC 308-4291

TITLE: Preparation of .beta.-alanine derivatives for use as **integrin inhibitors**

INVENTOR(S): Holzemann, Gunter; Goodman, Simon; Jonczyk, Alfred; Stahle, Wolfgang

PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany

SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048996	A2	20000824	WO 2000-EP969	20000208

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DE 1999-19907370 19990220
DE 1999-19957787 19991201

OTHER SOURCE(S): MARPAT 133:164332

AB The invention relates to novel .beta.-alanine derivs. [(I); Q, Q1, Q2, Q3 = CH, N; R = H, alkyl, aryl, halogen, OH, alkoxy, CF3, OCF3; R1 = H, alkyl; R2 = substituted phenyl; R3 = H, alkyl, halogen, OH, alkoxy, CF3, OCF3, CN, NH2, (di)alkyl amine, alkyl amide; R4 = H, (hydroxy)alkyl, alkyl ester, (un)substituted aralkyl; n = 2-6] and to their physiol. acceptable salts or solvates, useful in the treatment of diseases as selective .alpha.v.beta.3-, **.alpha.v.beta.5**-, or .alpha.v.beta.6-integrin inhibitors. Thus, 4-(trifluoromethoxy)-benzaldehyde, malonic acid, and ammonium acetate were reacted, and the product 3-amino-3-(4-trifluoromethoxyphenyl)propionic acid was esterified with thionyl chloride and methanol to give II. Glycine Me ester was condensed with 4-(4-methylpyridin-2-ylamino)butyric acid and the deesterified product reacted with II to give I [Q, Q1, Q2, Q3 = CH; R, R1 = H; R2 = 4-F3CO-C6H4; R4 = Me; n = 3], which was deesterified to the free propionic acid deriv. and converted to the sodium or trifluoroacetate salts. Title compds. can be used in the treatment of thrombosis, heart infarct, coronary heart diseases, arteriosclerosis, inflammations, **tumors**, osteoporosis, infections and restenosis after angioplasty or in pathol. processes induced or propagated by **angiogenesis**. Title compds. were tested for integrin inhibition in vivo in mice (no data).

L156 ANSWER 27 OF 41 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 2000:592558 CAPLUS

TITLE: Preparation of dibenzooxazepinones and related compounds as .alpha.v.beta.3, **.alpha.v.beta.5**, and/or .alpha.v.beta.6 **integrin** receptor **antagonists**.

INVENTOR(S): Patane, Michael A.; Newton, Randall C.

PATENT ASSIGNEE(S): Merck and Co., Inc., USA

SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

Searched by Barb O'Bryen, STIC 308-4291

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048603	A1	20000824	WO 2000-US3796	20000214

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-120564 19990217

AB Title compds. [I; U, V = N, CR6; .ltoreq.1 U = N, .ltoreq.1 V = N; W CO, SO2, CR1R2; X = O, S, SO, SO2, NR4, CR1R2; Y = (substituted) (CH2)0-4, (CH2)0-4O(CH2)1-4, (CH2)0-4NR4(CH2)1-4, (CH2)0-4SO(CH2)1-4, (CH2)0-4SO2(CH2)1-4, etc.; Z = (substituted) 5-6 membered monocyclic arom. or nonarom. ring system having 1-4 N, O, S atoms, 9-14 membered polycyclic ring system, wherein .gtoreq.1 of the rings is arom.; R1, R2 = H, halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, cycloalkylalkyl, cycloheteroalkylalkyl, aryl, aralkyl, aminoalkyl, acylaminoalkyl, alkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthioalkyl, carboxyalkyl, alkoxycarbonylalkyl, CF3; R4 = H, alkyl, alkenyl, alkynyl, aralkyl, alkoxyalkyl, cycloalkyl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, alkylcarbonyl, arylcarbonyl, etc.; R5 = H, alkyl, aryl, aralkyl, alkylcarbonyloxyalkyl, alkylaminocarbonylmethylene, etc.; R6 = H, halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, amino, etc.], were prepd. A soln. of 2-fluoronitrobenzene, Me 4- methoxysalicylate, and K2CO3 in DMF was warmed to 500 overnight to give Me 4-methoxy-2-(2-nitrophenoxy)-benzoate. The latter in MeOH was added to a suspension of 10% Pd/C in EtOH and treated with H2 at room temp. and pressure for 3 h to give Me 2-(2-aminophenoxy)-4-methoxybenzoate. This was stirred with NaH in THF to give 3-methoxy-10H-dibenzo[1,4]oxazepin-11-one, which was converted in several steps to [11-oxo-3-[3-(pyridin-2-ylamino)-1-propoxy]-11H-dibenzo[1,4]oxazepin-10-yl]acetic acid. Tested I at 1.mu.M gave .gtoreq.50% inhibition of attachment of .**alpha.v**.**beta.5**-expressing cells to vitronectin-coated plates.

REFERENCE COUNT: 4
REFERENCE(S):
(1) Murugesan; US 5420123 A 1995 CAPLUS
(2) Murugesan; Bioorganic & Medical Chemistry Letters 1995, V5(3), P253 CAPLUS
(3) Smithkline Beecham Corporation; WO 9845255 A1 1998 CAPLUS
(4) Smithkline Beecham Corporation; WO 9911626 A1 1999 CAPLUS

L156 ANSWER 28 OF 41 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:190942 CAPLUS
DOCUMENT NUMBER: 132:241952
TITLE: Pharmaceutical preparation containing a cyclic peptide and a chemotherapeutic agent or an **angiogenesis inhibitor**
INVENTOR(S): Jonczyk, Alfred; Perschl, Astrid; Goodman, Simon; Roesener, Sigrid; Haunschild, Jutta
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
Searched by Barb O'Bryen, STIC 308-4291

LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000015244	A2	20000323	WO 1999-EP6654	19990909
WO 200015244	A3	20000622		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

DE 19842415	A1	20000323	DE 1998-19842415	19980916
AU 9959758	A1	20000403	AU 1999-59758	19990909
PRIORITY APPLN. INFO.:			DE 1998-19842415	19980916
			WO 1999-EP6654	19990909

AB A pharmaceutical prepn. contg. the integrin **antagonist** cyclo(Arg-Gly-Asp-D-Phe-N-methylvalyl) (I) and/or salt thereof, .gtoreq.1 chemotherapeutic agent and/or salt thereof, and/or an **angiogenesis inhibitor** and/or salt thereof is useful for treatment of pathol. **angiogenic** disorders, thrombosis, cardiac infarct, coronary heart disease, arteriosclerosis, **tumors**, osteoporosis, inflammations, and infections. These agents may be administered as a combined prepn., sep. but simultaneously, or sequentially. Among the chemotherapeutic agents usable in combination with I are alkylating agents, antibiotics, antimetabolites, immunomodulators, hormones, hormone **antagonists**, mustard gas derivs., alkaloids, matrix **metalloproteinase inhibitors**, and protein kinase **inhibitors**. Thus, in mice 8-10 wk old inoculated with Lewis lung carcinoma cells on day 0, treatment with I (30 mg/kg/day i.p. beginning on day 4) and 5-fluorouracil (30 mg/kg/day i.p. beginning on day 7) slowed **tumor** growth.

L156 ANSWER 29 OF 41 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:144722 CAPLUS
DOCUMENT NUMBER: 132:185454
TITLE: Use of anti-**angiogenic** agents for inhibiting vessel wall injury
INVENTOR(S): Brown, Charles L., III; Gorlin, Steve
PATENT ASSIGNEE(S): Global Vascular Concepts, Inc., USA
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000010552	A2	20000302	WO 1999-US19218	19990824

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,

CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9956871	A1	20000314	AU 1999-56871	19990824
PRIORITY APPLN. INFO.:			US 1998-97579	19980824
			WO 1999-US19218	19990824

AB Use of anti-**angiogenic** agents to inhibit an undesirable response to vessel wall injury, including stent neointima, dialysis graft neointima, vascular graft-induced neointima, and the treatment of benign hypertrophic scar formation as well as the treatment and passivation of unstable atherosclerotic plaques are provided. The invention provides for the use of catheter-based devices for enhancing the local delivery of anti-**angiogenic** agents into the endothelial tissues of blood vessels of the living body.

L156 ANSWER 30 OF 41 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:404839 CAPLUS
DOCUMENT NUMBER: 131:58814
TITLE: Naphthyridine derivatives of pyrrolidinylpropionic acid and analogs useful as **integrin** receptor **antagonists**
INVENTOR(S): Duggan, Mark E.; Meissner, Robert S.; Perkins, James J.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 188 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9930709	A1	19990624	WO 1998-US26539	19981214
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9917257	A1	19990705	AU 1999-17257	19981214
US 6066648	A	20000523	US 1998-212123	19981215
PRIORITY APPLN. INFO.:			US 1997-69910	19971217
			US 1998-83251	19980427
			GB 1998-10182	19980513
			GB 1998-11283	19980526
			US 1998-92588	19980713
			WO 1998-US26539	19981214

OTHER SOURCE(S): MARPAT 131:58814

AB The invention relates to compds. and derivs. thereof, their synthesis, and their use as vitronectin receptor antagonists. Representative compds. include those of formula W-X-Y-Z-CR5R6-CR7R8-CO2R9 [W = (un)substituted formamidino or guanidino, or various (poly)cyclic groups; X = (un)substituted linear alkylene, or a carbo- or heterocyclic group; Y = (un)substituted linear alkylene or hetero derivs. thereof; Z = (un)substituted carbo- or heterocyclic group; R5-R8 = H or a wide variety of simple or complex substituents; R9 = H, alkyl, aryl, aralkyl, etc.]. More particularly, the compds. are antagonists of the vitronectin receptors .alpha.v.beta.3, .**alpha.v.beta.5**, and/or .alpha.v.beta.6, and are useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting vascular restenosis, diabetic **retinopathy**, **macular** degeneration, **angiogenesis**, atherosclerosis, inflammation, viral

disease, and **tumor** growth. The compds. typically display sub-micromolar affinity for integrin receptors, particularly .alpha.v.beta.3, **.alpha.v.beta.5**, and/or .alpha.v.beta.6 receptors (no data). For instance, the intermediate I (prepn. given) underwent a sequence of: (1) cyclocondensation with 2-amino-3-formylpyridine to form a 1,8-naphthyridine nucleus, (2) hydrogenation of the latter to a tetrahydro deriv.; and (3) alk. hydrolysis of the ester, to give two diastereomeric products II, which were sepd. by chromatog.

REFERENCE COUNT: 2
REFERENCE(S): (1) Bovy; WO 9506038 A1 1995 CAPLUS
(2) Okayama; JP 09-165370 1997 CAPLUS

L156 ANSWER 31 OF 41 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:718960 CAPLUS
DOCUMENT NUMBER: 131:346556
TITLE: Integrin-binding peptides and their use in therapy
INVENTOR(S): Ruoslahti, Erkki; Koivunen, Erkki
PATENT ASSIGNEE(S): La Jolla Cancer Research Foundation, USA
SOURCE: U.S., 29 pp., Cont.-in-part of U.S. Ser. No. 158,001.
CODEN: USXXAM

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5981478	A	19991109	US 1994-286861	19940804
WO 9514714	A1	19950601	WO 1994-US13542	19941122
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9512596	A1	19950613	AU 1995-12596	19941122
AU 682561	B2	19971009		
EP 730607	A1	19960911	EP 1995-903595	19941122
R: BE, CH, DE, DK, FR, GB, IT, LI, NL, SE				
JP 09509142	T2	19970916	JP 1994-515220	19941122
EP 906919	A2	19990407	EP 1998-250245	19941122
EP 906919	A3	19990421		
R: BE, CH, DE, DK, FR, GB, IT, LI, NL, SE				
US 5627263	A	19970506	US 1995-425238	19950418
PRIORITY APPLN. INFO.:			US 1993-158001	19931124
			US 1994-286861	19940804
			EP 1995-903595	19941122
			WO 1994-US13542	19941122

AB This invention is directed to novel integrin binding peptides. These peptides bind to .alpha.v- or .alpha.5-contg. integrins and can exhibit high binding affinity. They contain one of the following sequence motifs: RX1 ETX2 WX3 (esp. RRETAWA); RGDGX, in which X is an amino acid with a hydrophobic, arom. side chain; the double cyclic CX1CRGDCX2C; and RLD. The peptides generally exhibit their highest binding affinity when they assume a conformationally stabilized configuration, e.g., through cyclization via disulfide bonds. This invention also provides methods of therapeutic use of these peptides. These peptides may also be useful as substrates for attachment of integrin-bearing cells to surfaces such as prosthetic devices or in preventing the unwanted binding of cells to a target, such as the binding of osteoclasts to bone in the treatment of of osteoporosis; the inhibition of **angiogenesis**; and as

tumor inhibitors. Integrin-binding peptides were obtained by affinity purifn. of a phage display library contg. random sequences in the display cassette by panning with integrins. Peptides specific for several different classes of integrin were obtained.

REFERENCE COUNT: 25

REFERENCE(S):
(1) Anon; EP 503301 1992 CAPLUS
(2) Anon; WO 9201464 1992 CAPLUS
(3) Braatz; US 5091176 1992 CAPLUS
(4) Brooks; Science 1994, V264, P569 CAPLUS
(7) Fukuoka; Proc Natl Acad Sci 1992, V89(4), P1189 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L156 ANSWER 32 OF 41 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:509096 CAPLUS
DOCUMENT NUMBER: 129:136499
TITLE: Preparation of heterocyclic peptide derivatives as **integrin antagonists**
INVENTOR(S): Duggan, Mark E.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9831359	A1	19980723	WO 1998-US617	19980113
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9860231	A1	19980807	AU 1998-60231	19980113
US 6017925	A	20000125	US 1998-6626	19980113
EP 1007026	A1	20000614	EP 1998-903466	19980113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				

PRIORITY APPLN. INFO.:
US 1997-35614 19970117
GB 1997-2788 19970211
US 1997-62594 19971020
GB 1997-25996 19971209
WO 1998-US617 19980113

OTHER SOURCE(S): MARPAT 129:136499

AB Novel compds. X-Y-Z-Aryl-A-B [Aryl = 5-6 membered arom. ring contg. 0-3 N atoms and substituted with R8 and R9; X = NR1R2, NR1CR3:NR2, C(NR2R3):NR1, NR1C(NR3R4):NR2; aryl-NR1R2, aryl-C(NR2R3):NR1, aryl-NR1C(NR3R4):NR2, 5- to 6-membered (non)arom. ring contg. 0-4 N, O, or S atoms and substituted with R1-R4, 9-14 membered polycyclic ring contg. 0-4 N, O, or S atoms and substituted with R1-R4; Y = C0-8 alkylene, C3-10 cycloalkyl, C0-8 alkylene-Y1-C0-8 alkylene, (CH2)0-6-aryl-Y2-(CH2)0-6 alkylene; Y1 = NR10CO, CONR10, O, NR10, S(O)0-2, SO2NR10, NR10SO2, CO, CH(OR1); Y2 = bond, CO, CONR10, NR10CO; Z, A = independently (CH2)m, (CH2)m-Z1-(CH2)n; Z1 = O, NR11, NR11CONR12, CONR11, NR11CO, CO, C(S), S(O)0-2, SO2NR11, NR11SO2, CR11:CR12, C.tplbond.C; m, n = 0-6; B = (CR6R7)pCOR13; p = 1-3; R1-R5, R8-R12 = independently H, halo, C1-10 alkyl, aryl-C0-8 alkyl, amino-C0-8 alkyl, C1-3 acylamino-C0-8 alkyl, C1-6 alkylamino-C0-8 alkyl, C1-6 dialkylamino-C0-8 alkyl, aryl-C0-6 alkylamino-C0-6 alkyl, C1-4 alkoxyamino-C0-6 alkyl, etc; R6 = H, F, C1-8 alkyl, OH, C1-6 alkoxy, etc;

R7 = (un)substituted C7-20 polycyclyl-C0-8 alkyl-Q-amino-C0-6 alkyl; Q = SO2, CO, NHSO2, NHCO, O2C; R13 = OH, C1-8 alkoxy, C1-8 alkylcarbonyloxy-C1-4 alkoxy, L- or D-amino acid residue, etc.] and derivs. are described as vitronectin antagonists. The vitronectin receptor antagonist compds. of the present invention are .alpha.v.beta.3 antagonists, **.alpha.v.beta.5** antagonists or dual .alpha.v.beta.3/**.alpha.v.beta.5** antagonists useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting restenosis, diabetic **retinopathy**, **macular** degeneration, **angiogenesis**, atherosclerosis, inflammation, viral disease, and **tumor** growth. Thus, peptide analog I was prepd. in several steps from protected (S)-2,3-diaminopropanoic acid, (-)-10-camphorsulfonyl chloride, and 4-[2-(1,2,3,4-tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoic acid (prepn. given). Test procedures to measure .alpha.v.beta.3 binding and bone resorption inhibiting activity are described.

L156 ANSWER 33 OF 41 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000137932 EMBASE

TITLE: Matrix metalloproteinase and .alpha.v.beta.3 integrin-dependent vascular smooth muscle cell invasion through a type I collagen lattice.

AUTHOR: Kanda S.; Kuzuya M.; Ramos M.A.; Koike T.; Yoshino K.; Ikeda S.; Iguchi A.

CORPORATE SOURCE: Dr. S. Kanda, Department of Geriatrics, Nagoya Univ. Graduate Sch. of Med., 65 Tsuruma-cho, Showa-ku, Nagoya 466-8550, Japan. kanda3@spice.or.jp

SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology, (2000) 20/4 (998-1005).
Refs: 48
ISSN: 1079-5642 CODEN: ATVBFA

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Smooth muscle cell (SMC) migration from the tunica media to the intima is a key event in the development of atherosclerotic lesions and in restenosis after angioplasty. SMCs require not only migratory but also degradative abilities that enable them to migrate through extracellular matrix proteins, which surround and embed these cells. We used a collagen type I lattice as a coating on top of a porous filter as a matrix barrier in a chamber to test the invasive behavior of SMCs in response to a chemoattractant (invasion assay) and compared that behavior with simple SMC migration through collagen type I-coated filters (migration assay). Inhibitors of matrix metalloproteinase, KB-R8301, tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), TIMP-2, and peptide 74, attenuated platelet- derived growth factor-BB (PDGF-BB)-directed SMC invasion across the collagen lattice, whereas no effect was seen with these inhibitors on simple SMC migration through collagen-coated filters. RGD peptide inhibited SMC invasion but did not affect SMC migration. Anti-.alpha.v.beta.3 integrin antibody attenuated PDGF-BB-directed SMC invasion, whereas other antibodies against RGD- recognizing integrins, namely **.alpha.v.beta.5** and .alpha.5, had no effect. None of these antibodies had any effect on simple SMC migration. RGD peptide and anti- .alpha.v.beta.3 antibody inhibited the attachment and spreading of SMCs on denatured collagen but not on native collagen. These findings indicate that there is a difference in the mechanisms between simple SMC migration across a collagen- coated filter and SMC

invasion through a fibrillar collagen barrier. A proteolytic process is required for SMC invasion, and the degradation of matrix proteins alters the relationship between matrix protein molecules and SMC surface integrins.

L156 ANSWER 34 OF 41 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999126303 EMBASE
TITLE: .alpha.(v).beta.3 integrin binding affinity and specificity of SM256 in various species.
AUTHOR: Mousa S.A.; Lorelli W.; Mohamed S.; Batt D.G.; Jadhav P:K.; Reilly T.M.
CORPORATE SOURCE: Dr. S.A. Mousa, Du Pont Pharmaceuticals Company, Experimental Station, 141 and Henry Clay Road, Wilmington, DE 19880-0400, United States
SOURCE: Journal of Cardiovascular Pharmacology, (1999) 33/4 (641-646).
Refs: 28
ISSN: 0160-2446 CODEN: JCPCDT
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB This study was undertaken to define the .alpha.(v).beta.3 binding affinity and specificity of the low-molecular-weight nonpeptide integrin antagonist, SM256. SM256 demonstrated high potency (IC50, 0.057 .+-. 0.030 nM) in inhibiting vitronectin binding to purified human .alpha.(v).beta.3 receptors. Additionally, SM256 inhibited .alpha.(v).beta.3-mediated human umbilical vein endothelial cell (HUVEC) or 293/.beta.3 (.beta.3-transfected cell line) adhesion to fibrinogen with IC50 values of 0.0054 .+-. 0.0058 and 0.0023 .+-. 0.0012 .mu.M, respectively. SM256 demonstrated a relatively high degree of specificity for human .alpha.(v).beta.3-mediated functions as compared with other human integrins including .alpha.(v).beta.3 (IC50, 0.92 .+-. 0.69 .mu.M), .alpha.(11b).beta.3 (IC50, 0.72 .+-. 0.07 .mu.M), .alpha.4/.beta.1 (IC50, >100 .mu.M) and .alpha.5/.beta.1 (IC50, 2.3 .+-. 2.1 .mu.M). SM256 demonstrated different degree of species specificity in blocking .alpha.(v).beta.3-mediated cellular adhesion with relatively higher affinity to dog (IC50, 0.005 .+-. 0.002 .mu.M), rabbit (IC50, 0.021 .+-. 0.01 .mu.M), mouse (IC50, 0.035 .+-. 0.01 .mu.M), and pig (IC50, 0.41 .+-. 0.24 .mu.M) endothelial or smooth-muscle cell .alpha.(v).beta.3-mediated adhesion. Additionally, SM256 demonstrated high degree of .alpha.(v).beta.3 specificity as compared with .**alpha**.(v).**beta.5**, .alpha.5.beta.1, or .alpha.(11b).beta.3-mediated binding in these species. SM256 is a potent .alpha.(v).beta.3 antagonist with high affinity and specificity for .alpha.(v).beta.3- mediated functions. Additionally, a comparable .alpha.(v).beta.3 affinity for SM256 was demonstrated with endothelial cells obtained from various species (dog, mouse, rabbit, and pig) as compared with that from human.

L156 ANSWER 35 OF 41 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999243155 EMBASE
TITLE: Depletion of .alpha.V integrins from osteosarcoma cells by intracellular antibody expression induces bone differentiation marker genes and suppresses gelatinase (MMP-2) synthesis.
AUTHOR: Koistinen P.; Pulli T.; Uitto V.-J.; Nissinen L.; Hyypia T.; Heino J.
CORPORATE SOURCE: J. Heino, MediCity Research Laboratory, University of Turku, Tykistokatu 6A, Turku, Finland. jyrki.heino@utu.fi
SOURCE: Matrix Biology, (1999) 18/3 (239-251).

Refs: 50
ISSN: 0945-053X CODEN: MTBOEC
PUBLISHER IDENT.: S 0945-053X(99)00022-0
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Integrin heterodimers sharing the common .alpha.V subunit are receptors for adhesion glycoproteins such as vitronectin and fibronectin. They are suggested to play an essential role in cell anchoring, differentiation, and survival. Here, we describe the construction of an expression plasmid coding for an intracellular single-chain antibody against .alpha.V integrin subunit. Saos-2 osteosarcoma cells transfected with this DNA construct showed an approximately 70-100% decrease in the cell surface expression of .alpha.V.beta.3 and .**alpha**.V.**beta**.**5** integrins as shown by flow cytometry. Intracellular antibody expression had no effect on the mRNA levels of .alpha.V integrin. Pulse chase experiments of metabolically labeled integrins showed that the translation of precursor .alpha.V integrin subunit was not affected. However, the maturation of .alpha.V integrins as glycoproteins was slow suggesting that the transport from endoplasmic reticulum to Golgi complex was partially prevented. Depletion of .alpha.V integrins from Saos-2 cells led to a decreased ability to spread on fibronectin and vitronectin. Furthermore, the expression of osteoblast differentiation marker genes, alkaline phosphatase and osteopontin, was induced and concomitantly the expression of matrix metalloproteinase-2 decreased. Thus, .alpha.V integrins seem to be important regulators of osteosarcoma cell phenotypes. Our data also indicate that the expression of intracellular antibodies is an effective strategy to study the significance of specific integrins for cell phenotype and differentiation.

L156 ANSWER 36 OF 41 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999205183 EMBASE
TITLE: Role of hypoxia and extracellular matrix-integrin binding in the modulation of angiogenic growth factors secretion by retinal pigmented epithelial cells.

AUTHOR: Mousa S.A.; Lorelli W.; Campochiaro P.A.
CORPORATE SOURCE: Dr. S.A. Mousa, Du-Pont Pharmaceuticals Company, Ep. Station, Rt 141 and Henry Clay Rd, Wilmington, DE 19880-0400, United States. shaker.a.mousa@dupontpharma.com

SOURCE: Journal of Cellular Biochemistry, (1 Jul 1999) 74/1 (135-143).
Refs: 45
ISSN: 0730-2312 CODEN: JCEBD5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
012 Ophthalmology
029 Clinical Biochemistry
LANGUAGE: English; English
SUMMARY LANGUAGE: English

AB The retinal pigmented epithelium (RPE) is a monolayer of polarized cells located between retinal photoreceptors and blood vessels of the choroid. The basal surface of RPE cells rests on Bruch's membrane, a complex extracellular matrix structure which becomes abnormal in several disease processes, including age-related macular degeneration (AMD). Ruptures or abnormalities in Bruch's membrane are frequently accompanied by choroidal neovascularization. Disturbed interaction of RPE cells with their extracellular matrix (ECM) could play a role in this process. The present study was undertaken to examine the complex interactions between hypoxia, integrin, and ECM in the regulation of RPE functions. Antibody blocking

experiments demonstrated that RPE cell adhesion to vitronectin is mediated primarily through .**alpha**.v.**beta**.**5** and adhesion to fibronectin occurs through .alpha.5.beta.1. RPE adhesion to immobilized laminin demonstrated highest level of non-RGD- mediated adhesion as compared to that with collagen IV or the RGD matrices such as vitronectin (.**alpha**.v.**beta**.**5**) , fibronectin (.alpha.5.beta.1), or thrombospondin (.alpha.5.beta.1 + .**alpha**.v.**beta**.**5**). Addition of soluble vitronectin, or fibrinogen to RPE cell cultures resulted in a small to moderate increase in VEGF and FGF2 in the media, while each of these growth factors was dramatically increased after addition of thrombospondin 1 (TSP1). In contrast, soluble fibronectin resulted in differential upregulation of VEGF but not FGF2. Similarly, immobilized TSP1 resulted in differential greater upregulation in VEGF but not FGF2 release from RPE as compared to other ECMs under either normoxic or hypoxic conditions. Additionally, Hypoxia resulted in a time-dependent increase in VEGF, but not FGF2 release in the media. RPE cells grown on TSP1- coated plates showed increased VEGF and FGF2 in their media compared to cells grown on plates coated with type IV collagen, laminin, vitronectin, or fibronectin. The TSP1-induced increase in secretion of growth factors was partially blocked by anti-.alpha.5.beta.1, anti-.alpha.v.beta.3, and anti-.**alpha**.v.**beta**.**5** antibodies indicating that it may be mediated in part by TSP1 binding to those integrins. These data suggest that alterations in oxygen levels (hypoxia/ischemia) and ECM of RPE cells, a prominent feature of AMD, can cause increased secretion of angiogenic growth factors that might contribute to the development of choroidal neovascularization. These data also suggest the potential modulatory role of VEGF release from RPE by ECM and .**alpha**.v.**beta**.**5** and .alpha.5.beta.1 integrins.

L156 ANSWER 37 OF 41 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97379564 EMBASE
DOCUMENT NUMBER: 1997379564
TITLE: Vascular indications for integrin .alpha.v antagonists.
AUTHOR: Samanen J.; Jonak Z.; Rieman D.; Yue T.-L.
CORPORATE SOURCE: J. Samanen, Department of Medicinal Chemistry, Cardiovascular Med. Chem., Smith Kline Beecham Pharmaceuticals, 709 Sweden Road, King of Prussia, PA 19406, United States
SOURCE: Current Pharmaceutical Design, (1997) 3/6 (545-584). Refs: 420
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 002 Physiology
018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB During early investigations into the biology associated with the platelet integrin .alpha.IIb.beta.3, monoclonal antibodies to .alpha.IIb.beta.3 indicated that an .alpha.IIb.beta.3-like integrin was expressed on endothelial cells, smooth muscle cells and on a variety of cancer cell lines. That integrin became known as the vitronectin receptor. It was shown to contain the same .beta.3 subunit as .alpha.IIb.beta.3, but it contained a different alpha subunit, named .alpha.v. Instead of a large family of .beta.3 integrins, a large family of .alpha.v integrins was discovered. To date, the family includes .alpha.v.beta.1, .alpha.v.beta.3, .**alpha**.v.**beta**.**5**, .alpha.v.beta.6 and

USE - Used to inhibit bone resorption, restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation, viral disease, tumor growth or metastasis (claimed)
Dwg.0/0

L156 ANSWER 39 OF 41 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-247457 [22] WPIDS
DOC. NO. CPI: C2000-075020
TITLE: Pharmaceutical preparation for treating e.g. **tumors**, thrombosis or inflammation, contains cyclic **pentapeptide integrin inhibitor** and chemotherapeutic agent and/or **angiogenesis inhibitor**.

DERWENT CLASS: B04 B05
INVENTOR(S): GOODMAN, S; HAUNSCHILD, J; JONCZYK, A; PERSCHL, A; ROESENER, S
PATENT ASSIGNEE(S): (MERE) MERCK PATENT GMBH
COUNTRY COUNT: 86
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
DE 19842415	A1	20000323	(200022)*		5
WO 2000015244	A2	20000323	(200023)	GE	

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

AU 9959758 A 20000403 (200034)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 19842415	A1	DE 1998-19842415	19980916
WO 2000015244	A2	WO 1999-EP6654	19990909
AU 9959758	A	AU 1999-59758	19990909

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9959758	A	Based on	WO 200015244

PRIORITY APPLN. INFO: DE 1998-19842415 19980916

AB DE 19842415 A UPAB: 20000508
NOVELTY - A pharmaceutical preparation contains a combination of a specific cyclic **pentapeptide** (I) with a chemotherapeutic agent (II) and/or an **angiogenesis** inhibitor (III).
DETAILED DESCRIPTION - A pharmaceutical preparation contains (a) the cyclic **pentapeptide** of formula cyclo-(Arg-Gly-Asp-D-Phe-NMe-Val) (I) and/or its salt with (b) one or more of chemotherapeutic agents (II), **angiogenesis** inhibitors (III) and their salts.
INDEPENDENT CLAIMS are included for:
(i) the use of (I) and (II) and/or (III) (all optionally as salts), successively or in physical combination, for the preparation of a medicament for **tumor** treatment;
(ii) the use of (I) and (II) (both optionally as salts), successively or in physical combination, for **tumor** treatment; and
(iii) a kit comprising separately packaged (I) and (II).

ACTIVITY - Cytostatic; antithrombotic; cardiovascular; antiarteriosclerotic; osteopathic; antiinflammatory; ophthalmological; **antiarthritic**; antirheumatic; gastrointestinal; antipsoriatic; antibacterial; antiviral; antifungal; renal.

A protocol for testing antitumor activity against transplanted Lewis lung carcinoma in mice is described, but no results are given.

MECHANISM OF ACTION - **Integrin inhibitor**.

USE - Use of the preparation is claimed for treating pathological **angiogenic** disease, thrombosis, cardiac infarction, coronary heart disease, arteriosclerosis, **tumors**, osteoporosis, inflammation and infection. Specific disorders to be treated include apoplexy, angina pectoris, ophthalmological diseases (e.g. diabetic **retinopathy**, **macular degeneration**, myopia, ocular **histoplasmosis** or rubeotic **glaucoma**), rheumatoid **arthritis**, **osteoarthritis**, inflammatory bowel disease (e.g. ulcerative colitis or Crohn's disease), atherosclerosis, psoriasis, restenosis after angioplasty, viral, bacterial or fungal infections and acute renal failure.

ADVANTAGE - The combination of (I) (an **integrin inhibitor** described in EP770622) with (II) and/or (III) has better properties (no details given) than prior art medicaments for treating the same conditions .

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L156 ANSWER 40 OF 41 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-116764 [10] WPIDS
DOC. NO. NON-CPI: N2000-088390
DOC. NO. CPI: C2000-035725
TITLE: New **peptide inhibitors** of **integrins**, used for treating, e.g. **angiogenic**-based diseases.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): HUSE, W D; LEE, B A; PALLADINO, M A; VARNER, J A
PATENT ASSIGNEE(S): (IXSY-N) IXSYS INC
COUNTRY COUNT: 82
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9965944	A1	19991223	(200010)*	EN	96
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9881437	A	20000105	(200024)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9965944	A1	WO 1998-US12392	19980615
AU 9881437	A	AU 1998-81437	19980615
		WO 1998-US12392	19980615

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9881437	A	Based on	WO 9965944

PRIORITY APPLN. INFO: WO 1998-US12392 19980615
AB WO 9965944 A UPAB: 20000228
NOVELTY - **Peptide inhibitors** of **integrin** alpha-V, beta-3 and **alpha**-V, **beta-5** are new.
DETAILED DESCRIPTION - (A) A novel amino acid (aa) sequence comprises the binding domain (I) which binds integrin alpha v beta 3:
Thr-Cys-X1-X2-Arg-Ala-Asp-Cys-X3 (I)
INDEPENDENT CLAIMS are also included for the following:
(1) an aa sequence comprising the binding domain (II) which binds integrin alpha v beta 3;
(2) a **peptide** mimetic of sequences (I)-(VI);
(3) identifying a compound which binds integrin alpha v beta 3 and/or **alpha** v **beta 5** comprising selecting a compound to have a structure which mimics the binding domain of an amino acid as in sequences (III)-(VI):
Arg-Cys-Gly-Gly-Asp-Ser-X4-Cys-Tyr (II)
Thr Cys Glu Cys Arg Ala Asp Cys Tyr Cys (III)
Thr Cys Ser Pro Arg Ala Asp Cys Ala (IV)
Arg Cys Gly Gly Asp Ser Met Cys Tyr (V)
Arg Cys Gly Gly Asp Ser Asp Cys Tyr (VI)
ACTIVITY - Opthalmological; Vasotropic; Antiarteriosclerotic; Anti-**angiogenic**, Cytostatic; Antiinflammaroy; Antirheumatic; **Antiarthritic**; Antipsoriatic; Osteopathic.
MECHANISM OF ACTION - The **peptides inhibit** the binding of ligands to **integrin** alpha v beta 3 expressed on a cell in a subject and inhibit the function of alpha v beta 3. **Peptides** are tested for their ability to inhibit the ability of alpha v beta 3-expressing melanoma cells to adhere to ligands. The assay was carried out using **fibrinogen** coated wells and M21 melanoma cells. A particularly desirable **peptide** is one with an activity of 2- mu M or below.
USE - The **peptides** can be used for treating and preventing alpha v beta 3- and **alpha** v **beta 5**-mediated disease, e.g. inflammatory disorders such as immune and non-immune inflammation, chronic articular rheumatism and psoriasis, rheumatoid **arthritis**, disorders associated with inappropriate or inopportune invasion of vessels such as diabetic **retinopathy**, **neovascular glaucoma**, **macular degeneration**, capillary proliferation in atherosclerotic plaques and osteoporosis, cancer associated disorders such as solid **tumors**, solid **tumor** metastases, angiofibromas, skin cancer, retrolental fibroplasia, **retinopathy** of prematurity, hemangiomas, Kaposi's sarcoma, like cancers that require **neovascularization** to support **tumor** growth, undesirable smooth muscle cell migration/proliferation), occlusion of blood vessels after angioplasty (restenosis) and osteoclast-mediated bone resorption, e.g. osteoporosis. The **peptides** can also be used in a diagnostic method or kit for detecting a disease that involves the alpha v beta 3 integrin receptor. The compounds can be used to screen for other compounds, including **peptide** and non-**peptide** (small molecule) compounds, that can compete for binding to alpha v beta 3 integrin receptor and/or **alpha** v **beta 5** integrin receptor. The **peptides** can also be used for the production of antibodies.
ADVANTAGE - None given.
Dwg.0/1

L156 ANSWER 41 OF 41 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-610580 [52] WPIDS
DOC. NO. CPI: C1999-177732
TITLE: New integrin receptor antagonists.
DERWENT CLASS: B05
Searched by Barb O'Bryen, STIC 308-4291

INVENTOR(S): ASKEW, B C; COLEMAN, P J; DUGGAN, M E; HALCZENKO, W; HARTMAN, G D; HUNT, C A; HUTCHINSON, J H; MEISSNER, R S; PATANE, M A; SMITH, G R; WANG, J; HUNT, C
PATENT ASSIGNEE(S): (MERI) MERCK & CO INC
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9931061	A1	19990624	(199952)*	EN	249
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AU AZ BA BB BG BR BY CA CN CU CZ EE GD GE HR HU ID IL IN IS JP KG KR KZ LC LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK SL TJ TM TR TT UA US UZ VN YU					
AU 9918220	A	19990705	(199952)		
US 6048861	A	20000411	(200025)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9931061	A1		WO 1998-US26484	19981214
AU 9918220	A		AU 1999-18220	19981214
US 6048861	A	Provisional	US 1997-69899	19971217
		Provisional	US 1998-83209	19980427
		Provisional	US 1998-92622	19980713
			US 1998-212082	19981215

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9918220	A	Based on	WO 9931061

PRIORITY APPLN. INFO: US 1998-92622 19980713; US 1997-69899 19971217; GB 1998-7382 19980406; US 1998-83209 19980427; GB 1998-11295 19980526; US 1998-212082 19981215

AB WO 9931061 A UPAB: 19991210
NOVELTY - Integrin receptor antagonists (I) are new.
DETAILED DESCRIPTION - Integrin receptor antagonists of formula X-Y-Z-C(R5)(R6)-C(R7)(R8)-CO2R9 (I) and their salts are new.
Full definitions are given in the definition field below.
An INDEPENDENT CLAIM is included for compositions comprising (I) and an active ingredient selected from:
(a) an organic bisphosphonate or a salt or ester;
(b) an estrogen receptor modulator;
(c) a cytotoxic/antiproliferative agent;
(d) a matrix **metalloproteinase** inhibitor;
(e) an inhibitor of epidermal derived, fibroblast-derived or platelet-derived growth factors;
(f) an inhibitor of VEGF;
(g) an inhibitor of Flk-1/KDR, Flt-1, Tck/Tie-2 or Tie-1;
(h) a cathepsin K inhibitor; and/or
(i) a prenylation inhibitor, e.g. farnesyl transferase inhibitor or geranylgeranyl transferase inhibitor or a dual farnesyl/geranylgeranyl transferase inhibitor.
ACTIVITY - None given.
MECHANISM OF ACTION - Integrin receptor antagonists (alpha v beta 3, **alpha** v **beta 5** and/or alpha v beta 6).
USE - (I) are used for inhibiting bone resorption, treating or

preventing osteoporosis, and inhibiting vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, wound healing, viral disease, tumour growth and metastasis. (I) can be administered with other active agents.
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